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(71) Applicants and
(72) Inventors: **VIRTANEN, Jorma** [US/US]; 19211 Edgehill, Irvine, CA 92612 (US). **VIRTANEN, Jukka** [US/US]; 19211 Edgehill, Irvine, CA 92612 (US).

(74) Agent: **TEJINDER, Singh**; Klein' O'Neill & Singh, LLP, 2 Park Plaza, Suite 510, Irvine, CA 92614 (US).

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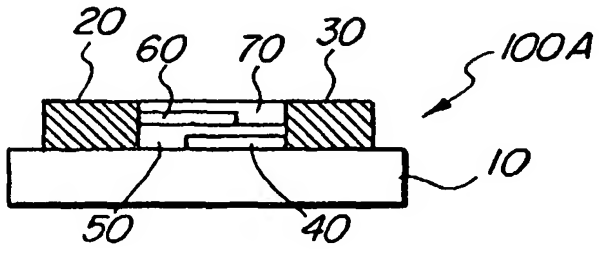

(57) Abstract: A capacitive device for measuring at least one electrical property is provided. The device includes a first conducting layer (40); a second conductive layer (60); wherein the first and second layers (40, 60) are operationally coupled to a measuring device for measuring at least one electrical property that depends on a physical and/or chemical factor; and a third layer (50) separating the first and second conducting layer (40, 60).

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METHOD AND APPARATUS FOR NANO-SENSING

CROSS REFERENCE TO RELATED APPLICATIONS

This application is related to the provisional U.S. patent application entitled, "METHOD AND APPARATUS FOR NANO-SENSING", Serial No. 60/340,811, filing date, 12/12/2001, the disclosure of which is incorporated herein by reference, in its entirety.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to sensors, and more particularly, to nanosensors.

2. Background

Nanosensors are small devices that are capable of detecting and responding to certain stimuli, wherein the sensing part is limited to a nanometer scale at least in one dimension. Stimuli may include biological and chemical substances, displacement, force, mass, acoustic, thermal or electromagnetic. Most nanosensors measure observables (as

defined below) such as concentration of a chemical, temperature, pressure or acceleration within a given frame of reference.

Nanosensors may be used for various bio-medical applications, for example, in-vivo, i.e. within the body; and/or intra-cellular; in-vitro, i.e. exterior to the body; disease detection; cellular repair; drug delivery; and measurement of pH and various minerals and/or elements, for example calcium, sodium, potassium, oxygen, glucose, and magnesium.

Nanosensors may also be used for detecting various types of vapors, for example methanol, ethanol, 2-propanol, acetone and toluene. Nanosensors may also be used for detecting airborne chemical/biological agents, for example, the anthrax bacteria. Nanosensors may also be used in communications and various industrial applications.

Some examples of electro-chemical detection methods are provided in the following incorporated herein by reference, in entirety:

US Patent No. 4,444,892: Malmros. "Analytical Device Having Semiconductive Organic Polymeric Element Associated With Analyte-Binding Substance"

US Patent No. 4,218,298: Shimada et al."Selective Chemical Sensitive FET Transducer"

US Patent No. 4,859,306: Siddiqi et al. "Selective-Ion Permeable Dry Electrodes For Analyzing Selected Ions In Aqueous Solutions"

US Patent No. 4,945,045: Forrest et al. "Electrochemical Methods of Assay"

US Patent No. 4,920,047: Giaver et al. Electrical Detection Of The Immune Reaction

US Patent No. 5,156,810: Ribi et al., "Biosensors Employing Electrical, Optical And Mechanical Signals"

US Patent No. 5,284,748: Mroczkowski et Al "Method For Electrical Detection Of A Binding Reaction"

WO 95/15971 and 96/40712: Meade et al.

US Patent No. 6,060,023: Maracas. "Molecular Sensing Apparatus"

US Patent No. 6,100,045: Van Es et al. "Detection of Analytes Using Electrochemistry"

Publications:

J. Wang "Electroanalytical Techniques in Clinical Chemistry and Laboratory Medicine", VCH, New York, 1988. QD115W246e 1988

W.F. Smyth, "Voltametric Determination of Molecules of Biological Significance", John Wiley&Sons, New York, 1992.

Examples of disposable and self-contained clinical chemical devices as well as important methods of their fabrication and use are provided in the following that are incorporated herein by reference, in entirety:

US Patent No. 3,799,742: Coleman. "Miniaturized Integrated Analytical Test Container"

US Patent No. 5,053,197: Bowen. Diagnostic Assay Module

US Patent No. 5,133,937: Frackleton et al. "Analysis System Having A Removable Reaction Cartridge And Temperature Control"

US Patent No. 5198368: Khalil et al. "Methods For Performing a Solid-Phase Immunoassay"

US Patent No. 5,217,905: Marchand et al. "Device And Method for the Rapid Qualitative and Quantitative Determination of the Presence of a Reactive Ligand in a Fluid"

US Patent No. 5,223,219: Subramanian et al. "Analytical Cartridge and System for Detecting Analytes in Liquid Samples"

US Patent No. 5,503,985: Cathey et al. "Disposable Device for Diagnostic Assays"

US Patent No. 5,580,794: Allen et al. "Disposable Electronic Assay Device"

US Patent No. 5,981,203: Meyerhoff et al. "Unitary Sandwich Enzyme Immunoassay Cassette, Device and Method of Use"

US Patent No. 5,714,390: Hallowitz et al."Cartridge Test System for the Collection and Testing of Blood an a Single Step"

Further examples of alternative detection methods in the prior art are (incorporated herein by reference, in entirety):

US Patent No. 4,313,929: Morita et al. "Method of Measurement of Antigens and Antibodies"

US Patent No. 5,427,915: Ribi et al. "Multi-optical Detection System"

US Patent No. 4,647,544: Nicoli et al. "Immunoassay Using Optical Interference Detection"

US Patent No. RE033581: Nicoli et al. "Immunoassay Using Optical Interference Detection"

US Patent No. 4,876,208: Gustafson et al. "Diffraction Immunoassay Apparatus and Method"

US Patent No. 5,089,387: Tsay et al."DNA Probe Diffraction Assay and Reagents"

Currently, nanosensors may be produced using porous silicon using various well-known processes, for example,

electrochemical etching, chemical vapor deposition and physical vapor deposition etc., and are discussed in the foregoing prior art patents and/or publications.

Current technological trend has been to miniaturize sensors. One reason for miniaturization is that a small sensor can often sense better than a large sensor. For example, the response time of a small sensor is often faster than that of a larger sensor. Also, small sensors reach equilibrium faster than large sensors. Furthermore, with modern micro-fabrication techniques the material cost of small sensors is minimal.

One example of a nanosensor is a "nanowire". A description of nanowires is provided in "Hydrogen Sensors and Switches from Electrodeposited Palladium Mesowire Arrays" by Fre´de´ric Favier et.al, published in the September 21, 2001 volume 293 of the "Science Magazine" incorporated herein by reference, in its entirety, (available via the Internet online at "sciencemag.org"). Nanowires however, have drawbacks, including, difficulty in large scale fabrication, controlled patterning, potential instability and contact problems.

Therefore, there is a need for nanosensors that are easy to fabricate, stable, robust and effective in nano-sensing.

SUMMARY OF THE PRESENT INVENTION

In one aspect, the present invention enhances miniaturization compared to the present state-of-the-art. The sensor(s) of the present invention may be electronic, and may be easily interfaced with processing and display devices.

In one aspect of the present invention, a capacitive device for measuring at least one electrical property is provided. The device includes, a first conducting layer; a second conductive layer; wherein the first and second layers are operationally coupled to a measuring device for measuring at least one electrical property that depends on a physical and/or chemical factor; and a third layer separating the first and second conducting layer. A part of the first and/or second layer is covered with a recognition molecule. The recognition molecule may be an antibody, antigen, oligonucleotide or a DNA fragment enzyme. Also, the third layer may function as an electric insulator, covered with a recognition molecule which may be an antibody, antigen, oligonucleotide or a DNA fragment enzyme.

In another aspect of the present invention, a method for fabricating a capacitive device for measuring at least one electrical property is provided. The method includes, depositing at least a first conducting layer operationally coupled to a conducting first lead; depositing a first spacer layer; and depositing at least a second conducting layer

operationally coupled to a second conducting lead, such that the second conducting layer is separated from the first conducting layer. The first spacer layer may be insulating, semi-conducting or of die-electric material.

The method includes depositing similar or dissimilar materials on the first and second conducting layers for building a conductive bridge between the first and second conducting layers.

In yet another aspect of the present invention, a capacitive device for sensing antigens is provided. The device includes a first conducting layer; and a second conducting layer separated by a spacer layer, wherein antibodies are placed on the spacer layer that attracts antigens.

In yet another aspect of the present invention, a capacitive device for testing DNA is provided. The device includes, a first conducting layer with at least a complementary probe; a second conducting layer with at least a second complementary probe; wherein the first and second conducting layers are separated from the first conducting layer by a spacer layer; plural soluble probes that are operationally coupled to the first and/or second complementary probe; and a conducting bridge formed by a DNA fragment that

is operationally coupled to the first and second complementary probe.

In one aspect, the present invention provides a device with plural layered structures, in which alternating layers have different conductivity, for example, in one implementation half the layers are metallic and the other half are insulating. In general, these layers are called conducting and spacer layers. The conducting layer may act as an electrode. The layers may be rectangular, and of the same size. However, because of the adaptive nature of the present invention, other shapes and sizes are well within the scope of this invention.

In one aspect, two alternating layers do not overlap completely. The layers form a pattern where one metallic layer may be shifted left and the other to right. The insulating layers may be centered. Thus, metallic layers to the right are electrically connected with each other. The same applies to the layers that are shifted to the left. The two metal layer packs are insulated from each other. Right and left sides are connected to electrical wires. Thus, the device may operate as a parallel capacitor.

Typically, the capacitor has two edges that are not in direct physical contact with the wires. One or both the edges may perform the sensing function. For that purpose the edges

may be etched and coated with various sensing molecules. The purpose is to change the capacitance or to make the capacitor leaky, when the capacitor is exposed to either chemical or physical observable(s). In addition to capacitance any other electrical property, such as voltage, impedance, conductance, current, or phase shift, may be measured.

In one aspect, the present invention allows an easy and low cost fabrication of nano-sensors. The dimensions and location of plural features are well controlled by fabrication methods that are already known in the art. The stability of a two dimensional layered structure is superior to that of fragile nanowires. The external contact for the nanosensors (hereinafter referred to as "nanoplates") may be produced in most implementations during fabrication. The size of the contacts may be adjusted from nanometer to millimeter scale.

It is a purpose of this invention to provide devices and associated methods, in which electrical properties of a multi-layered structure (also referred to as the "capacitive structure") are changed by external physical or chemical factors. The conductivity between the conducting layers may be increased and the capacitive structure made leaky by an external factor. Alternatively, in some implementations the original structure is a leaky capacitor, and the external

factor or stimuli may reduce the conductivity between the layers of the capacitor.

In one aspect of the present invention, the small size of the sensors makes it possible to place the sensors in unconventional places. For example, a biological sensor, according to one aspect of the present invention may be placed into or onto a needle. The sensed results will be obtained after the needle reaches the tissue or blood of a patient. There is no actual need to take a sample. The needle may be the only disposable part of the sensing device. The device may be totally self-contained so that it contains measurement, processing and display units. The information may be transferred to a permanent storage unit, such as a PC hard drive, before the disposal.

In another aspect of the present invention, the devices and methods may be used to measure the presence and concentration of analytes (defined below) suspected to be present in a sample or in a patient. The classes of analytes that may be measured include but are not limited to peptides, proteins, glycoproteins, oligonucleotides, DNA, RNA, steroids, lipids, lipoproteins, carbohydrates, and compounds that may be detected by electrochemical means.

Accordingly, it is an object of the present invention to provide a capacitive device, in which the capacitance or other

electrical properties are changed by an analyte, reactive or bound, on or near the edge of the device.

In another aspect of the present invention external particles are bound on or near the edge of the foregoing capacitive structure or device to induce a charge in the electrical properties of the structure. The particle may be conductive or it may be made conductive after the binding. The particles may have large dipole moment or be highly polarizable.

In another aspect of the present invention, the nanosensors may be implanted into the skin or some other organ. They may also be injected into circulation. The sensors may be very small, about the size of a cell, and actually placed inside a cell, if necessary. They may be made of materials, which are stable for years or alternatively dissolve in a body. Because of very small power consumption, a small battery may power the sensors. Information may be retrieved either using radio or microwaves. Alternatively, an external light may access an implanted sensor.

In another aspect of the present invention, an array of sensors may be implanted. Each sensor in an array may perform a different task.

In a related aspect of the present invention, the implanted sensor may be powered by a fuel cell that utilizes

chemicals that are abundant in a body. These chemicals may include glucose, cholesterol, ATP, and oxygen.

In another aspect of the present invention, the implanted sensor may be coupled with the nervous system of a patient. Most natural biochemical feed-back systems are independent of the nervous system. For instance, an increase in glucose concentration increases the production and secretion of insulin. Thus, biologically, it is not meaningful to couple chemo-receptor cells to the central nervous system.

Currently, our bodies are warned if there is excess pressure, heat, cold, light etc. It would be desirable to have continuous warning for every biochemical imbalance that is a serious threat to the well being of an individual. Like in the case of heat, there would be no feeling in the normal range, but immediately when something is out of normal physiological range, a conscious signal is obtained, the strength of signal is related to the magnitude of the deviation.

In one aspect of the present invention, by using the nanosensors, new possible senses may be created among humans. Humans would be conscious of any disease state at the onset. For example, a small cluster of cancer cells would be recognized immediately, and that would cause a conscious unpleasant feeling that would be only slightly unpleasant

early on, but will grow stronger if the cancer is allowed to grow. This would allow the detection of cancer years earlier than is currently possible.

A further aspect of the present invention provides devices and methods for food and water safety measurements, military, and anti-terrorist purposes.

This brief summary has been provided so that the nature of the invention may be understood quickly. A more complete understanding of the invention can be obtained by reference to the following detailed description of the preferred embodiments thereof in connection with the attached drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1D show various process steps to fabricate a nano-sensor, according to one aspect of the present invention.

Figures 2A-2D show various process steps to fabricate a nano-sensor, according to one aspect of the present invention.

Figures 3A-3C show various process steps to fabricate a nano-sensor, according to one aspect of the present invention.

Figures 4A-4J show various aspects of nano-sensors, shown in Figures 1A-1D, 2A-2C and 3A-3C, according to one aspect of the present invention.

Figures 5A-5F show a nano-sensor used with a testing needle, according to one aspect of the present invention.

Figures 6A-6B show a hydrogen sensor, according to one aspect of the present invention.

Figures 7A-7B show a localized attachment of oligonucleotide probes onto the nanosensor, according to one aspect of the present invention.

Figures 8A-8F show a capacitive structure with multiple conducting layers, according to one aspect of the present invention.

Figures 9A-9C show use of spin-coated particles, according to one aspect of the present invention.

Figures 10A-10F show a composite sensor structure, according to one aspect of the present invention.

Figures 11A-11C show the side view of Figure 8F, according to one aspect of the present invention.

Figures 12A-12B show use of magnetic patterns with the nano-sensors of the present invention.

Figures 13A-13B show affinity binding between conducting layers, according to one aspect of the present invention.

Figures 14A-14d show binding of bacteriophages, according to one aspect of the present invention.

Figures 15A-15B show formation of a conducting bridge with a DNA fragment, according to one aspect of the present invention.

Figure 16 shows circuitry for measuring voltage.

Figure 17 shows a circuit for measuring capacitance using the sensor of the present invention.

Figure 18 show multiple sensor modules, according to one aspect of the present invention.

Figures 19A-19B show a schematic representation of an implantable sensor, according to one aspect of the present invention.

Figures 20A-20C shows the implantable sensor of Figures 19A-19B coupled to a nerve cell, according to one aspect of the present invention.

Features appearing in multiple figures with the same reference numeral are the same unless otherwise indicated.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions:

"Analyte", any molecule that is in a sample and is being analyzed (assayed).

"Observable", any physical or chemical factor that can be measured either qualitatively or quantitatively. These include, but are not limited to light intensity and wavelength, temperature, acceleration, temperature, radioactive particles, humidity, chemicals, biochemicals, cells, and pathogens.

"Probe, oligonucleotide or DNA fragment" that is bound onto a solid support.

"Target, oligonucleotide or DNA fragment" that is in a solution before hybridization.

Figures 1A-1D show various stages of fabricating a nanosensor, according to one aspect of the present invention. Figure 1A shows a semiconductor substrate 10 with two electrical leads 20 and 30. Figure 1B shows a conductive layer 40, for example, a gold layer, deposited onto substrate 10 so that layer 40 is in contact with lead 20, but not with the lead 30. Thereafter, an insulating (also referred to herein as "spacer") layer 50 is deposited between leads 20 and 30.

Figure 1C shows a second conducting (e.g., gold) layer 60, which is deposited so that it is in contact with the lead 30, but not with the lead 20. Thereafter, a second spacer layer 70 is deposited on top of layer 60 and previously deposited spacer layer 50. It is noteworthy that the present invention is not limited to the foregoing two conducting and spacer layers, the adaptive nature of the present invention allows several deposition cycles that may be performed on substrate 10.

Figure 1D shows a top view of the sensor 100A shown in Figure 1C, with conductive layers 40 and 60 connected to leads 30 and 20, respectively.

In one aspect of the present invention, the layered structure discussed above and shown in Figure 1A-1D is grown onto a solid substrate 10 that can be of amorphous or crystalline material, for example, glass, quartz, silicon, mica, polyethylene, polyvinylchoride, or polycarbonate. Substrate 10 may be a composite or layered material. Substrate 10 may be flat and smooth, cylindrical, and/or patterned.

Leads 20 and 30 may be coupled to substrate 10 before deposition of layers 40, 50, 60 and/or 70, or they can be attached after all the foregoing layers are formed. Leads 20 and 30 may be evaporated onto substrate 10 or attached by epoxy or soldering.

If substrate 10 is of a semi-conducting material leads 20 and/or 30 may be created by doping a desired pattern on substrate 10. Approximately a distance of 10 nanometer ("nm") to 100 mm, or more advantageously between 500 nm and 1 mm may separate leads 20 and 30.

Both leads 20 and 30 may be made of the same or different material. Leads 20 and 30 may be made of gold, silver, copper, iridium, palladium, and platinum and/or other conducting materials which include in some applications indium tin oxide, and plastics, such as polyaniline, polythiophene, tetrathiafulvalene, and polyacetylene. Amalgams and composite

materials may also be used and are often more corrosion resistant, durable, and/or conductive than any pure element, for example, boron doped silver, several semiconductors, and other carbon composites.

Leads 20 and 30 may also be created by several methods as described in "The Mechanics of Solder Alloy Interconnects by Eds. Frear, Burchett, Morgan, and Lau" incorporated herein by reference, in its entirety.

Conducting layers 40 and 60 in sensor 100A may be made of the same materials as leads 20 and 30, i.e., any metal, semi-conductor, or photo-conductor.

Spacer layers 50 and 70, may be insulating or semiconducting, and may be fabricated from dielectric or semiconducting materials, provided that the material(s) in layers 50 and 70 are less conducting than layers 40 and 60. Examples of such materials without limitation are glass, quartz, silicon, cadmium selenide, mica, polyethylene, polyvinylchoride, polycarbonate.

Spacer layers 50 and 70 may also be made of composite materials, for example, polystyrene particles 70 that are optionally coated with a thin, approximately 20 nm, gold layer, dispersed onto a photo-resist(as shown in Fig. 9).

Spacer layers 50 and 70 may include polystyrene or other plastic particles pre-coated by evaporating a thin metal

layer. Alternatively, spacer layers 50 and 70 may be created by attaching approximately 1-20 nm gold particles by streptavidin-biotin or other similar bonding mechanism onto plastic particles and chemically depositing a gold or other metallic layer. These methods are well known in the art as discussed by Hayat, in "Immunogold Silver Staining", CRC Press, 1995, incorporated herein by reference, in its entirety.

Chemical deposition methods may be a part of fabricating sensor 100A in Figures 1A-1D, or when sensor 100A is used for detection.

Also other particles, such as bacteriophages 1110 and 1120 may be used as discussed below in context with Figure 14. Like spheres, bacteriophages 1110A and 1120A, may be affinity bound onto specified areas, especially onto the edge of sensor 100A. After silver, gold or some other metal staining, they provide thin elongated nanowires between plates. Carbon nanotubes, either single or multi-walled, may also be used to form conducting bridges between layers. The conductivity of carbon nanotubes is sensitive for many chemicals, especially for chemicals that are electron donors or acceptors (for example, ammonia and oxygen)

In one aspect of the present invention, sensor 100A may have different structures with different chemical

compositions. If spacer layers 50 and 70 contain conductive particles it is vertically conductive, which makes the entire structure 100A conducting. It is noteworthy that sensor 100A may not have bulk metal or conductor and is mostly surface, and accordingly, very sensitive to all kinds of physical and chemical factors. Sensor 100A may be made specific for a certain physical or chemical observable, as discussed below.

In several implementations of the present invention, spacer layers 50 and/or 70 are electric insulators. In these cases conductivity is created between layers 40 and 60 by an observable, for example, a conducting particle that may be bound between two conducting layers (40 and 60) by an affinity binding as shown in Figure 13. Particle binding by affinity methods is also well known in the art.

In one aspect of the present invention, sensor 100A is light sensitive. Electromagnetic field created by light can generate potential between adjacent layers 40 and 60. Also, spacer layers 50 and 70 may include light absorbing material that injects electrons on to conducting layers 40 and 60. These kinds of structures have applications beyond sensors.

In one aspect, sensor 100A may be utilized as solar cells converting light into electricity. When a light-receiving unit is small enough, only one photon at a time arrives into the unit, and the energy of that photon may be recovered. In

these implementations, semiconductors are advantageously added into sensor structure 100A. For example, layers such as p and n-doped silicon layers, or electric rectifier circuitry may be used to rectify the frequency of oscillating electric field of the light.

Sensor 100A may also be used to measure temperature by manufacturing layers 40 and 60 as bimetallic layers. The binding of a bimetallic layer changes the contact and conductivity between adjacent layers 40 and 60.

In another aspect of the present invention, attaching a small weight onto the edge of a conductive layer of sensor 100A imparts accelometric capacity. Bending of a layer, for example 40 and/or 60, due to acceleration changes the electrical properties, especially capacitance and conductance, of sensor 100A.

In one aspect of the present invention, conducting layers 40 and 60, and spacer layers 50 and 70 may be fabricated by evaporation, sputtering, chemical vapor deposition, deposition, atomic layer epitaxy, spin coating, adsorbing, or formed using some other method commonly known in the art. In another aspect the Langmuir-Blodgett method may also be used to fabricate sensor 100A.

In another aspect of the present invention, photo-chemical vapor deposition may be used to fabricate conducting

layers 40 and 60, and/or spacer layers 50 and 70. This process allows deposition at a relatively low temperature of plural elements, alloys, or ceramics. For example, without limitation, some of the elements that may be deposited are boron, carbon, aluminum, arsenic, cadmium, gallium, germanium, iron, mercury, indium, iridium, molybdenum, nickel, phosphorus, lead, platinum, rhenium, sulfur, antimony, selenium, silicon, tin, thallium, tellurium, and tungsten. Exemplary compounds include indium phosphide, silicon oxide, silicon nitride, aluminum oxide, zinc sulfide, zinc selenide, cadmium selenide, cadmium telluride, mercury telluride, gallium nitride, gallium phosphide, gallium arsenide, indium phosphide, indium antimonide,gallium aluminum arsenide, cadmium mercury telluride, yttrium barium copper oxide, and barium strontium titanate.

The foregoing elements and compounds include dielectrics, semiconductors, photoconductors, ferroelectrics, metallic conductors, and superconductors. Additional compounds and methods may be found in "Photochemical Vapor Deposition" by Egden, John Wiley, New York, 1992, "Chemical Vapor Deposition of Refractory Metals and Ceramics III" by Eds. Gallois, Lee, and Pickering, MRS, Pittsburgh, 1995, and "Ceramic Joining" by Schwartz, ASM International, 1990, incorporated herein by reference, in entirety.

In one aspect of the present invention, sensor 100A may include additional layers between conducting layers 40 and 60 and spacer layers 50 and 70. For example, an adhesive layer with chromium or incanal, may be deposited between conducting layer 40 and insulating layer 50, or between conducting layer 60 and spacer layer 70. Some of the surfaces may be activated chemically.

Furthermore, chemically active layers may also be included between conducting layers 40 and 60, and spacer layers 50 and 70, using oxygen, halogen, ammonia, or some other plasma treatment. The chemically active layer(s) may be used for recognition of certain molecules, as described below.

Also molecular layers may be adsorbed on plural layers of sensor 100A from gaseous, liquid, or liquid crystalline phase. Several traditional surface treatment chemicals are listed in "Index of Chemicals Used for the Treatment of Metal Surfaces" by Benninghoff, Elsevier, New York, 1974, incorporated herein by reference, in its entirety, that may be used.

Examples of other useful compounds that may be used to produce additional layers in sensor 100A are 6-hydroxyhexane thiol, and 6-aminohexane thiol that form a self-assembled monolayer onto gold and silver surfaces. Other techniques include silanization, which provides certain desired properties on surfaces (Virtanen et al., US 4,756,971,

incorporated herein by reference, in its entirety), for example, organosilanes and their hydrolytic polymers may be used as surface treatment agents in chromatography and electronics applications of sensor 100A.

Hydroxy group chemicals may also be used to make the surface(s) of sensor 100A hydrophilic, and amino group chemicals are useful for attracting various recognition molecules onto the sensing surface(s) of sensor 100A.

In one aspect of the present invention sensor 100A and the other embodiments described below may have two or several conducting layers like layer 40 and/or 60. All conducting layers may be made of the same material or several different materials may be used. The same applies to spacer layers, for example 50 and 70. The thickness of the plural layers may be approximately between 0.3 nm and 10 μm, and the approximate thickness between 5 nm and 500 nm is preferred.

The conducting and spacer layers may have different thickness. Also the thickness of the layers may vary. For example, half of the conducting layers (for example layer40 and/or 60) may be approximately 50 nm thick, while the other half may be approximately 200 nm.

In another aspect of the present invention, the thickness of the plural layers in sensor 100A increases incrementally, for example, from approximately 50 nm to 300 nm in

approximately 10 nm steps. These methods and structures may be used for multiplexing plural sensors, for example sensor 100A, to detect certain pre-defined observables.

For each assay particle, the particle size may be different and match the separation of the corresponding layers. Also some spacer layers may be conductive, while other layers are dielectrics. The same assay may be performed simultaneously at both of these sites to increase the dynamic range. For example, increasing conductivity from zero to some small but measurable value is very sensitive to a presence of an analyte, while a decrease in conductivity is not equally sensitive, but has utility of detecting higher concentrations of an analyte.

It is advantageous although not necessary to fabricate several sensing devices, for example sensor 100A, onto same substrate 10. Substrate 10 may be cut mechanically, for example, by a microtome that is designed to cut biological sample, or laser cutting may be used. Typically, the cutting laser's wavelength is short to avoid any excessive heating during the cutting process. However, the input cutting power must be high, to avoid excessive reflection from reflective layers.

During cutting, substrate 10 may smear plural layers of sensor 100A. To remove any possible debris, sensor 100A may

optionally be dipped in an etching solution. For example, if gold is used as a conductive material for layer 40 and/or 60, a potassium cyanide, or 6 M hydrochloric acid solution may be used for etching. Typically, the conductive layers of sensor 100A are etched for a short time.

In another aspect of the present invention, insulating layers (for example 50 and 70) are etched so that grooves are formed between conductive layers 40 and 60. The depth of the grooves may be between 1 nm and 100 μm approximately. The depth correlates with the separation of the adjacent conductive layers. Generally, the depth is less than the separation. However, in some embodiments, in which bending of conductive layers is a part of the sensing process, the depth may be several times the width of the gap.

In some implementations of the present invention, spacer layers 50 and 70 are composites containing particles. Entire spacer layer 50 and/or 70, except these particles, may be etched away. Etching method used depends on the insulating material. For example, silicon, glass, and quartz may be etched with hydrofluoric acid or ammonium fluoride, described by Hsiao, Virtanen, and Penner (1993) in Appl. Phys. Lett. 63: 1119-1121, incorporated herein by reference, in its entirety. Metal oxides may be dissolved with acids and some, like aluminum oxide, may be removed with potassium hydroxide.

In another aspect of the present invention, electro-osmosis accelerates etching by increasing concentration of the etching chemical.

It is noteworthy that plasma may create an oxide or halogenide that does not evaporate, and may be removed by an etchant, such as an acid. This provides a controlled removal of spacer layer 50 and/or 70. Most plastics may be dissolved by several organic solvents, such as acetone, methyl ethyl ketone, tetrahydrofurane, ethyl acetate, chloroform, toluene, or any mixture of the and other solvents.

In another aspect of the present invention, applying a potential between conducting layers 40 and 60 may generate electric field, and optionally external electrode(s) may be used as a part of sensor 100A. Most dielectrics, including elements, semiconductors, and plastics, are removed in a controlled way by an oxygen, halogen, argon, or some other plasma.

Figures 2A-2D show another aspect of the present invention where sensor 100B is similar to sensor 100A, except in this case, conducting layer 40A is deposited between leads 20 and 30, and a gap 80 is etched between leads 20 and 30. Spacer layer 50A is then deposited over layer 40A and thereafter, conducting layer 60 is deposited over layer 50A.

It is noteworthy, that layer 60A in this aspect does not touch leads 20 and/or 30.

Figures 3A-3C show yet another aspect of the present invention with sensor 100C having plural sensing areas, 10A, 10B and 10C, as shown in Figure 3D. Figure 3A shows substrate 10 with leads 20 and 30. Figure 3B shows a conducting layer 40B (similar to layer 40) with an etched gap 80A. Spacer layer 50B (similar to layer 50) is fabricated on layer 40B. Thereafter, as shown in Figure 3C, conducting layer 60B (similar to layer 60) is fabricated with etched gaps 90 such that gap 90 is opposite to gap 80A. Sensor 100C may have plural sensing regions, 10A, 10B and 10C. Electrical properties of each region 10A, 10B and 10C may be measured independently.

Figures 4A-4G show various implementations of the foregoing aspects of the present invention, as discussed above with respect to Figures 1A-1C, 2A-2C, and 3A-3C.

Figure 4A, shows the side view of sensor 100A described above. Figure 4B, shows etched spacer layer 50, such that conducting layers 40 and 60 are exposed.

In Figure 4C, another material 200 is electro-chemically or otherwise, deposited between conducting layers 40 and 60.

Figure 4D shows a metallic or other substance 210 deposited on conducting layer 40. In another aspect, the

metallic or other substance may be deposited on conducting layer 60.

Figure 4E shows two different materials 210 and 220 deposited on conducting layers 40 and 60, respectively. In another aspect, materials 210 and 220 may be substantially similar.

Figure 4F shows deposited materials 210 and 220 to be in contact with each other.

Figure 4G shows a conductive bridge 240 between conducting layers 40 and 60.

Figure 4H is the top view of Figure 4A, Figure 4I is the top view of Figure 4F and Figure 4J is the top view of Figure 4G with three conducting bridges 240, 250 and 260.

Figures 5A-5F show another aspect of the present invention that uses sensors 100A through 100C to detect various chemical or biological molecules or organisms, for example, the anthrax bacteria.

Figure 5A shows one aspect of the present invention, where sensors 100A, 100B and/or 100C may be used to detect observables or analyze certain analytes. Figure 5A shows needle 110 with deposited plural layers 120, 130 and 140 are, similar to layers 40, 50 and 60, described above. Figure 5B shows a system where a plastic or ceramic coating is applied

on needle 110. A small opening 180A is left to act as the sensing area.

Figure 5C shows a cross-section view with needle 110, plastic layer 150, conducting layer 120, spacer layer 130 and conducting layer 130.

Figure 5D shows another cross-sectional view based on Figure 5B with needle 110, plastic layer 150, conducting layer 120, spacer layer 130 and conducting layer 130.

Figure 5E shows the system of Figure 5D with electrical leads 160 and 170, similar to leads 20 and 30.

Figure 5E shows a system 180 with sensing area 180A. System 180 may include a micro-processor and measurement circuitry that is used to sense change in electrical or other properties of sensing area 180A.

In another aspect of the present invention, Figure 6A-6B show how sensor 100A may be used to detect hydrogen. Palladium 300 may be deposited between conducting layers 40 and 60. When palladium absorbs hydrogen (Figure 6B), the contact between palladium layer 300 and conducting layers 40 and 60 improves. Improvement in contact may be detected as measured current, voltage or other electrical characteristics.

Figure 7 shows an implementation of the Figure 4B structure to sense and/or detect DNA fragments. Figure 7A shows conducting layers 360, 370, 380 and 390, which are

similar to layers 40 and 60 in Figure 4B. Spacer layer 360A is etched (just like layer 50 in Figure 4B). Counter electrode 340 and layers 360 and 390 are negative, while layers 370 and 380 are positive. Oligonucleotides probes 350 are adsorbed on the exposed areas of conducting layers 360, 370, 380 and 390. Complimentary DNA fragments 350A are attracted to layers 370 and/or 380, as shown in Figure 15B.

Figures 8A through 8F show various other implementations of the sensors described above, according to one aspect of the present invention. Figure 8A shows conducting layer 40 deposited on substrate 10 with contact 410, similar to Figure 1C. Figure 8B shows a dielectric layer 530 deposited on layer 40. Multiple conducting layers as shown in Figures 8D to figure 8F may be fabricated with multiple contacts 410-520. Spacer layers 530, 620 and 630 separate plural conducting layers. Sensing area for sensing device 100D is 630A. It is noteworthy that plural conducting layers may be used to detect plural observables.

Figures 9A-9C show yet another aspect of the present invention where spin-coated particles are placed on conducting layer 40. Particles 700 in polymer suspension 710 are applied on conducting layer 40. Particles 700 may also include optional coating 750. Preferably, coating 750 may include gold. Excess polymer 710 may be etched as shown in Figure 9B,

and additional conducting layer 740 (similar to layer 60) may be deposited.

Figures 10A-10E show a composite structure 100E in which spacer layer, for example, layer 50, includes plastic particles 700. Figures 10B-10E show various steps by which multiple conductive layers, similar to layer 40 and 60 separated by spacer layers with plastic particles 700 may be fabricated. Figure 10E shows multiple conductive layers 40, 60, 810, 820 and 830, separated by spacer layers 50, 70, 810A, and 820, respectively. Figure 10E structure may be sliced into plural slices 840, as shown in Figure 10F.

In yet another aspect of the present invention, Figures 11A-11C show side view of Figure 10F with multiple conducting layers 40, 40, 40A and 60A separated by coated plastic particles 700. Figure 11C shows sensor 100F where anti-bodies 860 are attracted to plastic particles 700.

Spin coating of plastic particles as discussed above give a random distribution. In some applications, a regular distribution of particles is preferred. One such process is based on magnetic alignment, as discussed below.

Figures 12A-12B show another aspect of the present invention, that allows magnetic patterns using paramagnetic particles 900 and the sensing techniques of this invention.

Paramagnetic particles 900 are well known in the art and may be used as is or coated with a metal.

In Figure 12A, the magnetic field 900A is parallel to the surface of the paper. Magnetic particles 900 are separated by spacer layer 900C, which is similar to the spacer layers discussed above. If a magnetic field 900B, perpendicular to the paper plane is applied (Figure 12B), then the magnetic particles 700 are spread out, as shown in Figure 12B.

The density of rows or individual particles discussed may be adjusted by the strength of the magnetic field. If the field is perpendicular (Figure 12B) to substrate 10 and there is excess paramagnetic particles 900, columns of the particles are formed in a regular pattern.

While magnetic field is holding particles 900 in formation they may be coated chemically with silver, gold or some other metal as described by Hayat, in "Immunogold Silver Staining", CRC Press, 1995, incorporated herein by reference, in its entirety. This will fix structure 100G. The structure may also be fixed by affinity binding methods. In this case the surface and particles contain moieties, which are complementary or bind with a common target.

Figures 13A-13B show yet another aspect of the present invention using sensor 100H similar to sensor 100A, described above. Figure 13A shows conducting layers 40 and 60 separated

by spacer layer 50, wherein spacer layer includes antibodies 1020 that may be grown during fabrication. Particles 1000 are also coated with antibodies 1010, while the analyte in this example are antigens 1030.

An antigen 1030 binds itself to antibodies 1020 on the device and 1010 on the particle, hence closing the circuit between conducting layers 40 and 60. Sensor 100H, as shown in Figure 13B, operates as a capacitor.

Particles 1000 may be coated, at least partially, with recognition molecules 1010 (Fig. 13). Molecules 1010 are often charged. For example, oligonucleotides are negatively charged in all common buffers. A certain protein is negatively charged, if pH is above an isoelectric point and positively charged at a lower pH value. The charge is balanced by soluble counterions, which form an electrical double layer. It is noteworthy that these particles move when an electric field is applied. Also the particles may repel each other because of ξ-potential as described by J.N. Israelachvili in "Intermolecular and Surface Forces", Academic Press, London, 1985, incorporated herein by reference, in its entirety.

Particles:

The following provides a discussion on the various particles (700, 900 and/or 1000) that are described above with reference to plural aspects of the present invention

Gold particles may be used for the various applications described above, as metal particles, because of their stability in water, and constant size ranging from approximately 1 nm to 3 μm, which are commercially available. Also plastic particles, especially polystyrene spheres, between approximately 20 nm and 100 μm may be used and are also commercially available. Other commercially available particles include cellulose, silica, and diamond particles.

The quantitative interaction between charged colloidal particles is well known. The charge of the particles may be adjusted by attaching charged molecules, other than recognition molecules, onto the particles. Examples of charged molecules are polylysine, polyasparagine acid, polyallylamine, polyacrylate, histone, and DNA. Oligonucleotides and DNA may be used to adjust the charge in immunoassays and also in DNA testing, as described below. Typically, in DNA tests the DNA that is used to regulate the charge may not contain a target sequence.

Particle charge may also be regulated, for example, by pH, ionic strength, counter ions, solvent, and additives, such as polyethyleneglycol. Also charged molecules may be attached

on to the particles so that the binding is reversible. For example, if the surface of a particle is sparsely covered by negative moieties, such as carboxylates, an excess of a positive polymer, such as polyallylamine, will bind on to the surface and give the surface a positive charge. The negative charge of the carboxylates may be eliminated by adding acid so that pH is approxiately below 5. The binding of the positively charged polymer will be much weaker, and a significant part or possibly all of it will be detached from the particles.

It is also possible to change the charge by a chemical reaction. For example, the positive charge of amino groups may be eliminated by acylation that may be done in water by active esters, such as acyl N-hydroxysuccinimides.

Conductive particles, as described above, may also be charged with static electricity, which may be adjusted to be either positive or negative. The charge may also be changed during the assay. An additional charging electrode may added to give the particles a charge before they enter into the assay area.

Particle charge may be utilized in many ways in assays, in various aspects of the present invention. First, particles may be forced to move electrically through a sample, and while

they are moving their recognition molecules interact with the sample and collect analyte molecules.

Second, the particles may be attracted on to the surface of one electrode. By alternating the charge of two conducting layers, the particles may be concentrated on to the edges of certain layers. The binding kinetics of particles is faster because of concentration and the physical contact induced by the electric field. Notably, the present adaptive aspects allow the use of nearby conductive layers for attraction, while the layer that is coated with affinity molecules is electrically idle. This avoids electrochemical reactions of the affinity molecules and the sulfur-gold bond that is often used to bind affinity molecules.

Third, by removing the particles by a reversed electric field, and by attracting particles between other layers, or by changing the charge of the particles, the strength of an analyte mediated binding may be measured. This tests the specificity of the binding. Specific and non-specific binding in immunoassays may be differentiated. Moreover, the binding force may also be measured. For example, in DNA tests this allows to differentiate SNPs (Single Nucleotide Polymorphisms).

Fourth, the charge of the particles may be adjusted independently of an analyte. The charge may be even opposite

to that of an analyte. For example, DNA binding particles may be made positively charged. After interacting with a sample these particles may be attracted on to the negative electrode surface. The soluble DNA in the sample as well as DNA that is weakly bound on to the particles would be repelled from the electrode.

Particle based assays are common in biological testing as described in the following and incorporated herein by reference:

US Patent No. 5,616,467: Olsen, "Method and Kit for Analyte Detection Employing Gold-sol Bound Antibodies".

US Patent No. 4,459,361: Gefter, "Ligand Assay With One Or Two Particulate Reagents And Filter"

US Patent No. 4,853,335: Olsen, "Colloidal Gold Particle Concentration Immunoassay"

US Patent No. 6103538: Kotsugai, "Colloidal Gold Immunoassay Method"

US Patent No. 5079172: Hari et al., "Method For Detecting The Presence Of Antibodies Using Gold-Labeled Antibodies And Test Kit"

US Patent No. 5334538: Parker et al., "Immunoassay System and Device"

US Patent No. 6127130: Gol sol, "Multiassay Method For Determining The Concentrations Of Antigens And

Interferants"

Werthen and Nygren, "Effect of Antibody Affinity on the Isotherm of Antibody Binding to Surface-Immobilized Antigen", J. Immunol (Methods 115 (1988) 71-78) incorporated herein by reference, in its entirety.

Immunoassays:

The following provides a description of using plural aspects of the present invention in Immunoassays. Antibody-antigen interaction may be used in many different ways either to bind or prevent the binding of particles onto the surface of an electrode. In a traditional sandwich type assay one member of a matching antibody pair is bound on to particles and the other on to an electrode. The corresponding antigen forms a bridge between two antibodies and binds the particle on to the surface of the electrode as depicted in Figures 13A-13B. In this approach an antigen is a large enough molecule to have at least two spatially separated epitopes. Most proteins may be assayed by sandwich assay.

Several variant of this basic method are summarized here. If the particles (described above) are conducting, the conductivity between conductive layers, (for example, 40 and 60) will increase. If the particles are non-conducting, it will change the capacitance of the sensing device (e.g. 100A).

Non-conducting particle may be made a conductor by depositing metal layer onto its surface. This method may also be used in conjunction with conducting particles to improve the contact between the particle and the conducting layers. If the particle is a photo-conductor, exposure to optical light will increase its conductivity. If the conducting layers are connected with conducting bridges, the conductivity will decrease due to the binding of an analyte or a particle.

A cleavable spacer provides another way to perform a sandwich assay, Virtanen US Patent No. 6,312,901, which is incorporated by reference in its entirety. The number of the bound conductive particles is directly proportional to the concentration of the antigen.

For smaller molecules, such as steroids and several drugs, competitive assay may be used. The antibody is attached, for example, on to a particle, and the antigen or an analog of the antigen is attached onto the electrode (Figure 13B). The antigens in the sample saturate the antibody molecules on the particles. The competitive assay is not as sensitive as the sandwich assays, because zero and very small concentrations of the antigen gives maximum or near maximum binding. Small changes are very difficult to differentiate from normal experimental error.

Currently the preferred electrode material (for example, 40 and/or 60) is gold. Gold surface may be first coated with streptavidin, which will adsorb spontaneously from an aqueous solution. Biotinylated antibody will bind with steptavidin providing a good coating. Several other ways of attaching antibodies onto the gold surface are well known in the art. These include forming a monolayer of polylysine or copolymer of lysine and cysteine on to the gold surface, and attaching periodate oxidized antibody in the presence of sodiumcyanoborohydride on to this monolayer.

Another method is to reduce the antibody with dithiotreitol or with some other reductant and allow the reduced antibody to chemisorb directly on to the gold surface.

A wide variety of immunoassays may be performed using the various sensors and processes under the present invention. For example, without limitation, hCG (pregnancy test), prostate specific antigen (PSA) detection, insulin, proinsulin, glucagon, glycated hemoglobin, growth hormone, fetoprotein, TSH, C-reactive protein, CK-MB, myoglobin, troponin, interferons, interleukins, ferritin, tumor negrosis factor, trypsin, plasminogen, cardiolipin, cortisol, aldosterone, estradiol, digoxin, benzodiazepine, vancomycin, amphetamine, cocaine, morphine, tetrehydrocannabinol, phenobarbital, secobarbital, parathione, adenovirus,

chlamydia, cytomegalovirus, hepatitis viruses, HIV, influenza, and parainfluenza.

The following provide details reagrding immunoassays and panels, incorporated herein by reference, in entirety:

US Patent No. 5,744,358: Jackowski, "Method And Device For Diagnosing And Distinguishing Chest Pain In Early Onset Thereof"

US Patent No. 5,075,220: Pronovost, "Determination Of Chlamydial or Gonococcal Antigen Using A Positivley-Charged Ionically Binding Support"

US Patent No. 5,030,561: Donahue et al., "Chlamydia Assay Using Amidine Modified Supports or Particles"

US Patent No. 4,497,900: Abram, "Immunoassay for Neisseria Gonorrhoeae Antigens"

US Patent No. 4497899: Armstrong, "Immunoassay for Chlamydia Trachomatis Antigens"

Kohler et al., "Antigen Detection to Diagnose Bacterial Infections", Boca Raton, Florida, CRC Press, Inc. 1986, pp. 138-144.

Figures 14A-14D show yet another aspect of the present invention, where sensor 100J similar to 100A in Figure 1D, and 100J in Figure 4G, is used for binding bacteriophages 1110A and 1120A to complimentary molecules 1130 and 1140,

respectively. Proteins 1110 are a part of bacteriophage 1110A and protein 1120 are a part of bacteriophage 1120A.

Figure 14A shows molecules 1130 and 1140 attached to spacer layer 50 between conducting layers 40 and 60. It is noteworthy, that more than one pair of conducting layers 40 and 60 may be used.

Figure 14B shows complementary molecules 1130 and 1140 bound with bacteriophages 1110A and 1120A.

Figure 14C shows particles 1150, similar to particles 700 bound to bacteriophages 1110A and 1120A.

Figure 14D shows sensor 100J that is similar to the sensor 100I in Figure 4G, where a conductive bridge 1160 (with particles 1150) are created between conducting layers 40 and 60.

Metal coated bacteriophages 1110A and 1120A may be used to operate as thin elongated nanowires between conducting layers 40 and 60.

Testing DNA:

Figures 15A-15C shows, yet another aspect of the present invention with sensor 100K similar to sensors in Figure 1A and 4G using DNA fragment 1220. Complementary probes 1200 and 1210 are placed between conducting layers 40 and 60 respectively. Soluble probes, 1230, 1240, 1250 and 126, with gold particles

1270 (similar to particles 700) are coupled to complementary molecules, as shown in Figure 15B.

Figure 15C shows conductive bridge 1280 between conducting layers 40 and 60, similar to sensor 100I in Figure 4G.

DNA fragment 1220 may act as a template for conducting bridge 1280 that functions as a nanowire. DNA fragments of interest bound on probes 1200 and 1210, while the entire DNA strand 1220 is hybridized by 1230-1260 to get a continuous metal coating, to provide conductive path 1280 that may recognize multiple events. (E. Brown et al. (1998) Nature 391:775, incorporated herein by reference in its entirety) The use of gold particles may be avoided by ligation of the probes together. Thus, a continuous DNA duplex is an electric conductor (as described by D. Porath et al. Nature 403:635, incorporated herein by reference in its entirety). Weak conductance can be detected, for example, by measuring leakage current of the capacitor.

The following discussion, according to one aspect of the present invention is based on sensor 100K described above and shown in Figure 15C. As shown in Figure 15C, DNA fragment 1210 is bound between the conductive layers 40 and 60 with the stationary probes 1200 and 1210. Soluble probes 1230-1260, contain at least one gold particle that may cover most of DNA

fragment 1220, if the sequence has complementary segments. After a gold or silver amplification a continuous wire 1280 is created between the conductive layers 40 and 60. If the sequences do not match, there will be gaps and no conductivity is detected.

The present invention allows testing of plural sequences simultaneously. The main large-scale application of oligonucleotide arrays is comparative expression analysis. Gene expression patterns in healthy as well as in diseased tissues and cells will greatly increase the understanding of the function of living organisms. The effect of drugs may be understood in much more detail than presently.

Another application for the oligonucleotide arrays is the finding of single nucleotide polymorphisms (SNPs). It is estimated that in human genome one out of a thousand nucleotides is polymorphic. These SNPs are the main reason for human diversity. Once the SNPs have been characterized and correlated with certain disease states, SNPs can be used to predict an individuals tendency for many diseases including various cancers as described by Cole et al. (1999) in "The genetics of cancer-3D model", *Nature Genetics Supplement* 21: 38-41), "Heart Disease" by Lusis (2000) in "Atherosclerosis", *Nature* 407: 233-241), and alzheimers disease, incorporated herein by reference, in entirety.

Another example of DNA diagnostics is the detection of fetal DNA in maternal plasma as described by Lo (2000) , in "Clinical Chemistry", 46:1903-1906), incorporated herein by reference, in its entirety.

DNA and RNA studies are not limited to humans. Plant genomics has enormous economical importance. Knowledge of pathogen genes and gene expression may be used in diagnostics and for the design of new drugs.

Oligonucleotide probes, as discussed above, may synthesized so that they contain aliphatic amino, mercapto, or other groups. Mercapto groups have a drawback that they tend to be oxidized by a positive electrode (anode). The positive charge is sometimes used to attract sample DNA to the close proximity of the electrode.

Particles or analytes themselves are attracted to electrode(s). The charge of the particles may be opposite to the charge of an analyte. Even, when particles are partially covered by negatively charged oligonucleotide probes, which further bind negatively charged targets, the particles may be positively charged or electrically neutral. Thus, it is possible to use negative charge to attract these particles. In addition to stabilizing the sulfur-gold bond, the negative charge repels the oligonucleotide probes on the surface of the anode.

Typically, probes 1200 and 1210 will be nearly perpendicular to the surface and easily accessible (Fig. 15A). In this case when positive charge is used, the probes are likely to lay flat on the surface being sterically hindered.

Probes 1200 and/or 1210 may have 5 to 10,000 nucleotides, and preferably 10 - 80 nucleotides. Long probes have generally genomic origin. The target is often a PCR product. Other amplification methods may be used, including isothermal and ligation amplification. The probes should have preferably about the same length as the amplicons.

Hybridization as shown in Figure 15C is well known in the art. Temperature should preferably be 20 °C below the melting temperature of the dublex. The salt concentration effects the melting temperature and kinetics of the hybridization. The melting temperature depends also on guanidine and cytidine contents of the probes and the target.

A higher salt concentration in the buffer and higher C/G-content will increase the melting temperature. Typically electric current will increase the temperature of the elecrolyte.

Power input is given by $P=VI$, where V is the potential and I is the current. The increase in the temperature is $\Delta T=VIt/Cm$, where t is the time and C is the thermal capacity of the medium of a mass m. A certain thin layer of walls may

be included into mass m. The method of the present invention is less sensitive to external conditions than the most currently used methods. This is due to the electric field that may be utilized to increase the rate of the hybridization as well as to test the stringency of the hybridization.

Polymerase and ligase chain reactions as well as isothermal amplification may be performed using sensors of the present invention. The temperature cycling (not for isothermal) may obtained by electric potential induced heating between the electrodes or by embedding heating elements near the electrochemical cells. The heating is more effective, if instead of a direct current, an alternating current is used.

Oligonucleotide analogs, such as peptidenucleotide acids (PNAs), and thionucleotide acids, also offer increased stability and/or stringent hybridization.

Oligonucleotide probes may be prehybridized with complementary oligonucleotides. The purpose of this kind of array is to study interaction of biomolecules with double helical DNA.

Cell and Pathogen Detection:

Cells and pathogens may be detected either by assaying certain surface markers, or their DNA. The methods already described above for immunoassays and DNA testing are applicable. The particles may also be bound onto the cell

membrane, either before or after they are bound onto the surface of an electrode. Examples of cells include the human T&NK cells (CD2 and CD7), T helper cells (CD4), T cells (CD5), supressor cells (CD8), E. Coli, Salmonelle, and Helicobacter pylori.

Electro-chemical Methods:

Figure 16 shows an example of a circuit that may be used for measuring voltage. Circuit 1300A includes capacitor 1300F and resistor 1300E within module 1300 that gets input voltage 1300B. Voltage 1300C is measured at resistor 1300D. Parallel resistor 1300E and capacitor 1300F are analogous to the capacitive sensors, described above.

Figure 17 shows measurement of capacitance and leakage of capacitor 1320 coupled in parallel to module 1300. Transistor 1320A provides external charge to diode 1320B that powers capacitor 1320. Voltage 1300C may be measured by device 1330. It is noteworthy, that module 1300, in this figure is similar to the capacitive sensors, described above.

Input voltage (1300B in Figure 17) is a constant voltage source. A short pulse, for example 50 μs, is given to the base of a transistor 1320A. A very low leakage capacitor 1320 is charged *via* a diode 1320B. In parallel to capacitor 1320 is a leaking capacitor module 1300.

If conductive particles are bound between the conducting layers, voltage is measured through a high impedance Op-Amp module 1330 that contains field-effect transistors. Without the measurement cell the capacitor 1320 would retain over 99% of its charge. Leakage due to cell 1300 will reduce the charge and voltage exponentially. This reduction may be sampled at desired intervals or continuously. The time constant of the leakage may be correlated with the number of conductive particles. This circuitry is referred to herein as a "Charge-and-Leak Amplifier".

In another aspect of the present invention, Figure 18 shows plural modules 1300 with the circuit shown in Figure 17 and described above. The circuit of Figure 18 includes a switch 1400 that allows each subsystem of a sensor with various 1300 modules to be coupled to measuring device 1330.

The following discussion is based on using several electrochemical methods, which are known in prior art and discussed above with reference to the various figures including Figures 16-18.

In one aspect, the present invention utilizes primarily electrical measurements, for example, current, voltage etc. However, other detection schemes may supplement electrical detection. For example, when light is used in conjunction with photo-conductive materials, the light may be simultaneously

used to get additional information on an analyte, recognition molecules, substrate, or conductive particles. Reflectance, scattering, fluorescence, or some other optical property of the particles or an associated unit, such as liquid crystalline display may be measured.

As discussed above, the plural sensors of the various aspects of the present invention may contain several conducting layers in close proximity. In some implementations the potential of each layer may be independently controlled. This kind of device may serve as an electrochemical measurement device. Working, counter and reference electrodes may be a part of one device.

All traditional electrochemistry may be performed, but in addition, multiplexing different sensors provide more options, than conventional means. For example, potential sweep study may be done without actual potential sweep; if there are enough layers so that all data may be collected simultaneously. Possibly, the potential of each conducting layer (40 or 60 or their multiples) is changed only few millivolts to cover the range of several volts with the whole device. As a result electrochemical analytical techniques may be utilized.

The electrodes may be coated with enzymes, such as glucose or cholesterol oxidase. Hydrogen peroxide that is

released in the enzymatic reaction may be detected electrochemically. Examples of other small molecules that may be detected by enzymatic means are ethanol, lactic acid, and bilirubin described by Wieck et al. (1984) in "Anal. Chem." Acta 158: 137. Alternatively hydrogen peroxide may enzymatically oxidize many compounds, such as benzidine, tetramethyl benzidine, p-fluorophenol, or p-fluoroaniline to produce fluoride ion, or some other a secondary stable species that may be detected by an ion selective electrode.

In many cases the enzymes provide highly specific analytical method for their substrates. This widens the number of analytes significantly. Example of the compounds and groups of compounds that may be detected by electrochemical means are: cathecolamines, several drugs, oxygen, nitric oxide, nitrous oxide, carbon dioxide, nitro, nitroso, azo, heterocyclic compounds, isocyanates, phenols, amines, most sulfur containing compounds, such as disulphides, dithiocarbamates, thiobarbiturates, thioureas, thiols, sulphonates, sulphides, and sulphoxides, and also cations, anions, chelates, and organometallics.

The following references provide details of electrolytic detection techniques, incorporated herein by reference, in entirety:

US Patent No. 5401378: King et al., "Ionic Reservoir At

Electrode Surface"

US Patent No. 4758325: Kanno et al., "Ion Selective Electrode And Flow Type Ion Sensor Using The Same"

US Patent No. 4973394: Ross et al., "Immobilized Valinomycin Molecule For K^+ Sensor"

US Patent No. 5234566: Osman et al., "Sensitivity And Selectivity Of Ion Channel Biosensor Membranes"

Ammann, "Ion-Selective Microelectrodes: Principles, Design, and Application", Springer-Verlag, New York, 1986. QD571.A48 1986

A.L. Laskar and S Chandra, "Superionic Solids and Solid Electrolytes. Recent Trends", Academic Press, Inc., New York, 1989.

Measurement of Electrical Properties:

Typically, electrical power may be provided by a battery (Galvanic cell), fuel cell, solar cell, electromagnetic radiation, magnetic induction, direct contact with external power source, or by any other commonly known means.

Almost any electrical measurement device that is able to measure either voltage, current, capacitance, inductance, impedance, or phase shift may be a part of the various aspects of the present invention. (A.J. Bard and L.R. Faulkner "Electrochemical Methods: Fundamentals and Applications",

Wiley New York, 1980, QD553.B37), incorporated herein by reference, in its entirety.

Coupling electrical devices to computer processing units and to networks is well known in the art. Examples may be found in several books, including J.J. Barbarello "PC Hardware Projects, Volume 3" (Prompt Publications, Indianapolis, 1998); W.J. Tompkins and J.G. Webster "Interfacing Sensors to the IBM PC" (Prentice Hall PTR, Englewood Cliffs, 1998), S. McDowell and M.D. Seyer "USB Explained" (Prentice Hall, Upper Saddle River, 1999), and J. Axelson "Serial Port Complete" (Lakeview Research, Madison, 1998), incorporated herein by reference, in entirety. Networks include Local-Area-Networks, Wide Area Networks, and the Internet. Networks may also utilize among others, metal cables, fiberoptics, or be wireless. Various protocols/mechanisms may be used for data transfer, including without limitation, Bluetooth ® (an industry standard, published by the Bluetooth Standards Organization) and Infra Red standards, incorporated herein by reference, in entirety.

Direct detection of a tunneling current using the plural sensor devices, described above is one choice, but Charge-and-Leak Amplifier system described above and shown Figures 17 and 18 may also be used.

In the case of a direct contact between gold particles and electrodes, current may be too large, and hence resistors

are added in series with the gold particles. A sample-and-Hold Amplifier, as described in J.J. Brophy, Basic Electronics for Scientists, McGraw-Hill Publishing Co, New York, 1990, p. 234, incorporated herein by reference, in its entirety, may be modified so that it may be applied to measure electrical properties between pair of electrodes.

There are several commercially available personal computer cards and associated software packages that may convert a PC into an automatic electronic measurement device. The various electrical properties between any pair or combination of conductive layers may be automatically monitored.

Photo-electrochemical methods:

The following provides a description of one aspect of the present invention to use the plural sensors described above as photo-senstive device. A substrate, for example substrate 10, may be coated with a photoconductor. Light may be used to create conductive pathways in the photoconductive layer. Any area in the photoconductive layer may be selectively addressed.

In one aspect of the present invention, permanent patterning of various layers in the device is avoided. Instead light forms a temporary pattern as required. Light

may be patterned in several ways. For example, masks are a traditional way of selectively exposing some areas for light. Traditional masks are fixed, and they should be either stored or inserted into the sensor device.

Micro-mirror arrays provide a method for patterning of light that is programmable. Another way to accomplish programmable light pattern is to apply liquid crystal display technology. Instead of black color the back plate may be coated with reflective layer, or be transparent. In both cases the light would be directed only to certain areas on substrate 10.

If substrate 10 is a non-conductor, shining light on to the photoconducting layer may create nanowires. However, if the photoconductor is on a metallic layer, only an area of interest needs to be lighted.

The area may be whole assay area, or it may be only a small part of it. The assay area may be scanned with a micrometer sized laser spot. This allows the localization of individual conductive particles, and also the measurement of the electrical properties of each particle individually.

Conductive particles, as described above, may be photo-conductive. Electrodes may be metallic, semi-conducting or photo-conducting in this case. The location of each particle may be found by scanning with a focused laser beam.

Implantable Sensors:

Figures 19A-19B show another aspect of the present invention, where sensor 100A, modified into sensor 100L, as discussed below, and operates as an implantable device for detecting plural analytes. Figure 19A shows electrodes 1710 and 1760 that are coated with enzymes, with conducting layers 40 and 60 (shown in Figure 19B). A liquid crystal area 1730 is also shown.

Figure 19B shows a cross-sectional view taken from the section shown in Figure 19A. Figure 19B shows conducting layer 60, plural liquid crystal areas 1730, 1740 and 1750. Sensing area for device 100L is shown as 1730A.

In one aspect of the present invention, microscopic sensors 100L may be fabricated. Sensor 100L may be smaller than one human cell, hence may be implantable. The power consumption of these sensors is so low that a very small battery may be used. Light such as laser light may be used to acquire information from sensor 100L.

In one aspect, a sensor and a liquid crystalline display may be coupled in series or parallel in a circuitry, as shown in Figure 19A or 19B. If they are parallel the potential in the LC display will decrease when the conductivity of the sensor increases. The situation is reversed in the serial coupling. The reflection from a flat LC display depends on

its orientation. To reduce orientation problem, the display may be cylindrical. However, in order to avoid orientation problem, the display may be spherical or at least hemispherical.

A spherical display may be fabricated by emulsion coating gold or some other metal coated plastic particle on a liquid crystalline material. A very thin, about 5-50 nm, metal layer, such as gold or silver layer is chemically deposited on top of the liquid crystalline layer. After drying the particles, an additional metal layer, about 50 nm, is evaporated onto one hemisphere of each particle. Immediately a dielectric layer is deposited on to the same hemisphere. After slightly etching the metal from the opposite hemisphere the process is complete. Short plasma etch or dissolution with organic solvent removes the liquid crystal and exposes the first gold layer in that hemisphere.

Using thiol chemistry these particles may be bound onto the substrate so that they are properly oriented. The dielectric protecting the upper hemisphere may be partially or totally etched away, allowing electrical contact with the upper metal hemisphere. Partial etching may be done, for example, by laser ablation.

Battery as a power source and LC display as a detector are well within the art. However, in the preferred

implementations power may be harnessed from biological energy of a body. In some implementations the nervous system of the body is utilized as a detector, as described below. In these ultimate implementations a cell sized sensor 100L is continuously powered by a biochemical energy of a body and a signal is transmitted into a nervous system and to a brain.

Biological fuel cells are well known in the art. The present invention describes a novel combination of fuel cells and sensors, and improvements of biologically powered fuel cells (Fig. 19). In a preferred embodiment, the chemical source of the energy is glucose. The concentration of the glucose is high and relatively stable. Glucose oxidase is a stable enzyme. Hydrogen peroxide is formed in the enzymatic oxidation of glucose.

Platinum electrode 1710 is preferred, because of the stability and minimal over potential in the reduction of the hydrogen peroxide. The counter electrode 1760 may be coated by a reducing enzymatic system. One preferred enzyme is cytochrome c oxidase that reduces oxygen to water.

The system may also contain cytochrome c that actually transfers the electrons from the electrode to the cytochrome c oxidase. This fuel cell utilizes abundant chemical species and relatively stable enzymes.

Encapsulating the electrodes in a polymeric matrix may further stabilize the enzymes. First, a reversed microemulsion of enzymes and polymerizable material, such as methyl methacrylate, is prepared in an organic solvent, for example, octane. Second, the monomer is polymerized. The microemulsion is adsorbed onto the electrode. The enzymes that are capsulated are often stable for years at ambient temperature.

Bio-Analyzer Coupled to Sensory Nervous System:

Figures 20A-20C show sensor 100M similar to the implantable sensor 100L of Figure 19B, according to one aspect of the present invention. Sensor 100M may be coupled to a nerve cell1 1900 with axon 1910. Figure 20A shows plural swicthes 1770-1800, coupled next to opening 1800-1840. Nerve cells grow via openings 1770-1800 and plural switches 1810-1840 are used to couple or de-couple a specific nerve cell electronically from sensor 100M.

Figure 20B is a side view of the device shown in Figure 20A, and Figure 20C shows nerve cell 1900 with axon 1910 growing through a hole.

Neurons and sensors may be connected by neural surgery as described by Agnew, McCreery, in "Neural Prostheses, Fundamental Studies", Prentice Hall, 1990), incorporated herein by reference, in its entirety. Alternatively, sensor

100M may contain cavities that slowly release nerve growth factors. Neurotrophic factors, such as NGFs stimulate neural growth, especially after peripheral nerve lesion (Grothe, Nikkhah Anat. Embryol (2001) 202: 171) incorporated herein by reference, in its entirety and furthermore direct the growth toward sensor 100M (Fig. 20C).

The nervous system consists of the central nervous and peripheral nervous system. Sensory nerves have a receptor at their end. Two main classes of receptors are exteroreceptors and enteroreceptors. Enteroreceptors measure observables, such as cholesterol, blood sugar and oxygen levels, and body temperature. These factors are very well controlled, although no conscious signal is given to the brain.

Exteroreceptors consist of photoreceptors, chemoreceptors, thermoreceptors, mechanoreceptors, and nocireceptors. Sensory nerves act as transducers converting sound, mechanical, photonic, chemical, or thermal energy into electrical signal.

The ion fluxes across nerve cell membranes form the basis of impulse propagation in the Hodgin-Huxley model of depolarization-repolarization wave in neuronal fiber (Hodgin, *Science* 145: 1148, incorporated herein by reference, in its entirety). During propagation there is an inward sodium ion and outward potassium ion flux.

During resting the potential of a membrane is approximately 50 mV, and the average action potential is about 110 mV. Usually, the signal is all-or-nothing. An impulse is initiated by increasing the membrane potential above a certain threshold value. The initiation may be done artificially. The nerve signal may be digital.

Receptor potential is graded, unlike the action potential, which is all or none. The magnitude of the receptor potential determines the frequency of the synaptic triggering, and thus the frequency of the pulses that are sent to the central nervous system.

Thermo-reception is also adaptable for chemical sensing, because temperature has low, normal, and high range. The proposed glucose bio-sensor (100M) could be anywhere in a skin, but preferably in an area that is protected by clothing. Temperature variations in the general area would not affect glucose sensing, because sensory system is sensitive to differentials.

In case of high glucose concentration, sensor area would feel warm or hot, depending on the glucose concentration. Low glucose concentrations would feel cool or cold. Normal glucose level would not give any conscious feeling. The actual temperature in the sensor area would not change, only the feeling of the temperature would depend on the glucose

concentration. The proposed methods to transduce glucose level into sensory nervous signal are the subject of this invention. Biological, biochemical and nanotechnological methods may be used to obtain that goal.

Information transmitted from the mechanoreceptors in the fingers enables us to feel the shape and the texture of objects. Mechanoreceptors in general are sensitive to touch. High pressure gives the feeling of a pain. There are only three synaptic relay sites between sensory receptors, and the skin and the cerebral cortex. Mechanoreceptors are connected to the caudal medulla, where they terminate in the cracile or cuneate nuclei. The second order neurons are connected to contralateral thalamus. The third-order neurons in the thalamus are finally connected to the primary somatic sensory cortex located in the postcentral gyrus of the parietal lobe. Somatic cortex contains four areas.

Two of the foregoing receive information from the skin and two from muscles and joints. These have been mapped in detail. For example, it is known, which part of somatic cortex is responsive for the stimulus in the right forefinger. Touch of a finger activates at least four areas in the somatic cortex, first one indicates that a finger has been touched (may be any finger, except a thumb), second tells in which hand this finger is, third gives the general area of the

finger (for example, the tip of a finger), finally the fourth defines the exact finger. These maps have been in animal studies using microelectrodes.

Humans may be studied by fMRI, PET scan, and magnetoencephalography (MEG). The information obtained by these techniques is useful and necessary during the development of the methods of this invention. It must be emphasized that the routine use of these sensing methods does not require any expensive and sophisticated instruments nor any other instruments, because the human nervous system itself would be sensing and reporting instrument.

Pain is an unpleasant sensory feeling associated with actual or potential tissue damage. Noxious insults to peripheral tissues activate nocireceptors. Nocireception do not necessarily lead to the perception of pain. This may have evolutionary explanation.

All tissue damage is harmful for an individual and for the species. However, if individual can not do anything to avoid or fix the situation, a consciousness of the problem does not help and may actually be harmful. These noxious insults include cancer and radiation damage.

Cancer typically starts to be painful when death is near. In the past any early warning had been useless and actually prevented an individual acting at full capacity. The

situation has reversed with the development of the modern medicine. If the pain due to cancer could be selectively amplified enormously, the cancer could be detected several years earlier than is possible currently. The situation is similar with radiation damage. If a person could feel even a small radiation damage (above the background radiation), that person could seek protection. It is a part of this invention to develop selective methods to increase pain. This increase can be transient or semipermanent, unless the reason is removed.

Some chemoreceptors are highly sensitive and specific to certain chemicals, while others like olfactory chemoreceptors are sensitive to a class of chemicals. Thermoreceptors are also sensitive to many chemicals. Menthol and eucalyptol have cooling sensations, while many alkaloids, especially piperidine containing, produce heating sensations.

Pain Perception:

In the CNS, pain is relayed by the thalamic nuclei (DM, AN, IL, and CM) and perceived by cingulate gyrus (ACGI and ACGII). Pain perception involves both "attention riveting" (selection) and "actual perception" (emotional aspect). Activation and de-activation of these centers can be followed in real time by functional Magnetic Resonance Imaging (fMRI). For example, insertion of an acupuncture needle into a pain

relief point causes first a transient signal in the thalamic nuclei and cingulate gyrus, but within seconds de-activates these centers. This demonstrates that a stimulus in a very small area (needle) may cause effects in the brain that are clearly discernible by fMRI. Thus, a point-like sensor may be effective enough to induce a signal that is detectable by a nervous system.

The following provides a few examples to fabricate the various sensors described above.

Example 1: Onto a flat and smooth glass plate (substrate 10) is sequentially evaporated layers of approximately 10 nm of chromium, approximately 200 nm of gold, and approximately 10 nm of chromium. The plate is then spin coated with approximately 150 nm layer of photo resist (Shipley Co). The plate is covered by a mask, and exposed to UV-light for approximately a min. The plate is then developed and baked.

Etching is performed with 6-M hydrochloric acid/nitric acid solution. The resist is washed away, although in some other applications the resist may serve as an insulating layer. An approximate 100 nm layer of silicon dioxide (layer 40) is deposited (chemical vapor deposition, CVD) so that it extends approximately 10 μm over the edges of the gold square, but does not cover the connecting wires.

A second chromium-gold-chromium layer (60) is deposited, and all other operations are repeated essentially the same way as in the first cycle. However, the mask is a mirror image of that used the first time.

The third cycle is identical to the first cycle, and similarly the fourth cycle is identical to the second one. Altogether six metal layers may be deposited. The plate is then spin coated by approximately 5 μm thick polystyrene layer.

The glass is cut automatically by a glass-cutting machine. The functional edge is etched for approximately 15 seconds with approximately 1 M hydrofluoric acid. These fabrication steps furnish a sensor base unit, as described above, which may be used for several purposes depending on the chemical treatment of exposed gold or silicon dioxide.

To fabricate a hydrogen detector, as shown in Figures 6A-6B, the exposed edges of the gold layers are immersed into palladium chloride/perchloric acid solution. Palladium is deposited electrochemically onto the gold edges using Platinum counter electrode and SCE reference electrode. About 300 mV potential is used until a weak conductivity is observed between the layers of the sensor. During deposition, the potential of all gold layers is the same. The potential is swept back and forth approximately 10 mV, every second to measure conductivity.

In the presence of hydrogen, palladium absorbs hydrogen, and swells. The contact and conductivity between the gold layers improve. The increase of the conductivity is relative to hydrogen concentration.

Example 2. The sensor unit of Example 1 is treated with aminopropyl triethoxysilane, which will activate the silicon dioxide bottom of each groove. Biotinyl N-hydroxysuccinimide will spontaneously conjugate with the amino groups. Streptavidine coated approximately 100 nm polystyrene particles are added. They will bind into the grooves.

When a colloidal solution of approximately 10 nm biotinylated gold particles are allowed to interact with plastic particles, they will be partially covered with gold particles. The unbound gold colloid is washed away. Gold chloride solution and hydroquinone is added. Gold may be deposited around the particles, which are bound onto the polystyrene spheres. Thus, nanowires are created between adjacent gold layers. Gold is coated with antibody molecules, which impart specific binding properties for the sensor. In the presence of antigen the conductivity of the device will change.

Example 3. Approximately 20 nm chromium and 200 nm gold layer are evaporated onto approximately 100 μm polyimide film. The film is coated with a suspension of approximately 1 μm

polystyrene particles, which are coated with streptavidine. A magnetic plate is brought from below onto close proximity with the substrate. A gold colloid of approximately 10 nm biotinylated particles is added. The solution on the top of the substrate is diluted and mostly removed. Gold chloride and hydroquinone solution is added. The plastic particles will be coated with gold. The surface is washed and dried. After spin coating with photoresist the excess of the photoresist is removed by oxygen plasma, so that the gold coated particles are just exposed. A new approximately 200 nm layer of gold is evaporated on top of the photoresist. The process is repeated plural times.

Another metal coated, approximately 100 μm polyimide film is glued on top of the pack of evaporated layers. The edge of the layered plate is cut with a mircotome so that it is straight. The plate is about 210 μm thick. The edge is glued onto long rod that may have a square cross section having approximate dimensions of 0.6 mm x 0.6 mm. This rod has at intervals of approximately 6 mm rectangular openings of approximate size 0.2 mm x 0.5 mm. Next an approximate 100 μm slice is cut with a microtome. This slice is already glued with one rod.

Another similar rod is glued with the open edge. The holes in both rods may match exactly each other. The rods should absorb UV-light so that when the assembly is now exposed to UV-light, only the photo resist that is aligned with the hole will react and may be dissolved with a photo resist developer. Developing is done very slowly. The photo resist between opposing holes is removed completely. The long rod is cut into approximately 6 mm long pieces so that the holes are in the center of each piece. The macroscopic wires are attached with conducting epoxy. When the recognition molecules are driven electrically though the layered structure, they will bind, and the sensor is ready for use.

While the present invention is described above with respect to what is currently considered its preferred embodiments, it is to be understood that the invention is not limited to that described above. To the contrary, the invention is intended to cover various modifications and equivalent arrangements.

What is claimed is:

1. A capacitive device for measuring at least one electrical property, comprising:

a first conducting layer;

a second conductive layer; wherein the first and second layers are operationally coupled to a measuring device for measuring at least one electrical property that depends on an external physical and/or chemical factor; and

a third layer separating the first and second conducting layer.

2. The capacitive device of Claim 1, in which a part of the first and/or second layer is covered with a recognition molecule.

3. The capacitive device of Claim 2, wherein the recognition molecule is an antibody.

4. The capacitive device of Claim 2, wherein the recognition molecule is an antigen.

5. The capacitive device of Claim 2, wherein the recognition molecule is an oligonucleotide or a DNA fragment.

6. The capacitive device of Claim 2, wherein the recognition molecule is an enzyme.

7. The capacitive device of Claim 1, wherein the third layer may function as an electric insulator.

8. The capacitive device of Claim 7, wherein at least a part of the third layer is covered with a recognition molecule.

9. The capacitive device of Claim 8, wherein the recognition molecule is an antibody.

10. The capacitive device of Claim 8, wherein the recognition molecule is an antigen.

11. The capacitive device of Claim 8, wherein the recognition molecule is an oligonucleotide or a DNA fragment.

12. The capacitive device of Claim 8, wherein the recognition molecule is an enzyme.

13. The capacitive device of Claim 1, includes plural conducting pairs are separated by a dielectric layers.

14. The capacitive device of Claim 13, wherein the plural conducting layers may be between 3-5000.

15. The capacitive device of Claim 1, wherein the measuring device is a LCD.

16. The capacitive device of Claim 1, wherein a conducting bridge is formed between the first and second layer by binding a conductive particle between the first and second conducting layer.

17. The capacitive device of Claim 16, wherein the conducting bridge is a DNA duplex that is formed by ligation of probes that are bound by a target DNA between the probes.

18. The capacitive device of Claim 16, wherein the conductive bridge is formed by gold or silver deposition using DNA bound gold colloid template.

19. The capacitive device of Claim 1 is implantable with enzyme coated electrodes operationally coupled to the first and second conducting layers.

20. A method for fabricating a capacitive device for measuring at least one electrical property, comprising:

depositing at least a first conducting layer operationally coupled to a conducting first lead;

depositing a first spacer layer; and

depositing at least a second conducting layer operationally coupled to a second conducting lead, such that the second conducting layer is separated from the first conducting layer.

21. The method of Claim 20, further comprising:

depositing a second spacer layer over the second conducting layer.

22. The method of Claim 20, wherein the first spacer layer may be insulating, semi-conducting or of dielectric material.

23. The method of Claim 21, wherein the second spacer layer may be insulating, semi-conducting or of dielectric material.

24. The method of Claim 20, further comprising:

depositing similar or dissimilar material on the first and second conducting layers for building a conductive bridge between the first and second conducting layers.

25. The method of Claim 20, further comprising:

depositing palladium between the first and second conducting layers used for detecting hydrogen.

26. The method of Claim 20, wherein antibodies may be attached on the first spacer layer for detecting antigens.

27. A capacitive device for sensing antigens, comprising:

a first conducting layer;

a second conducting layer separated by a spacer layer, wherein antibodies are placed on the spacer layer that attracts antigens.

28. A capacitive device for testing DNA, comprising:

a first conducting layer with at least a complementary probe;

a second conducting layer with at least a second complementary probe; wherein the first and second conducting layers are separated from the first conducting layer by a spacer layer;

plural soluble probes that are operationally coupled to the first and/or second complementary probe; and

a conducting bridge formed by a DNA fragment that is operationally coupled to the first and second complementary probe.

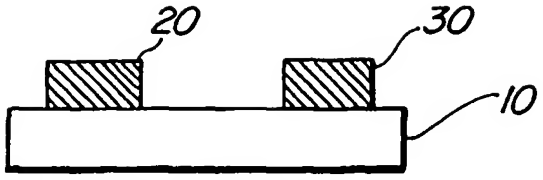


FIG. 1A

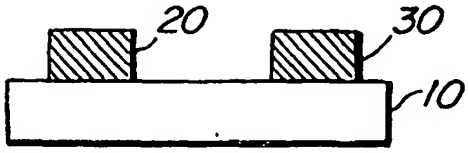


FIG. 2A

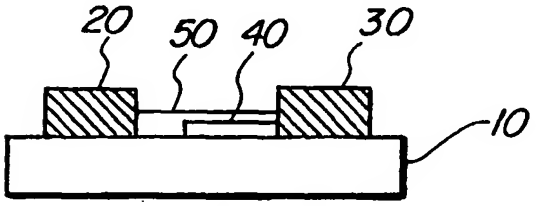


FIG. 1B

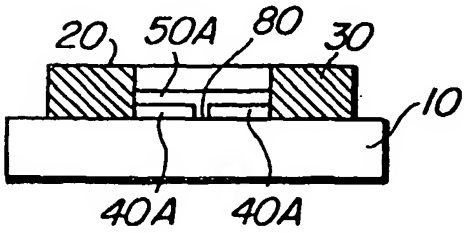


FIG. 2B

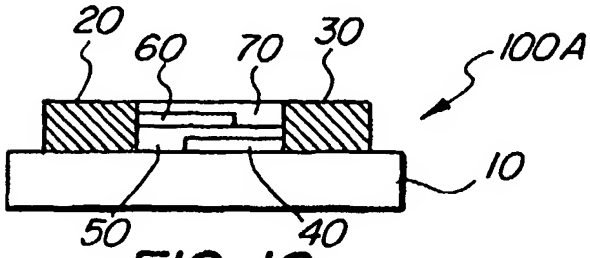


FIG. 1C

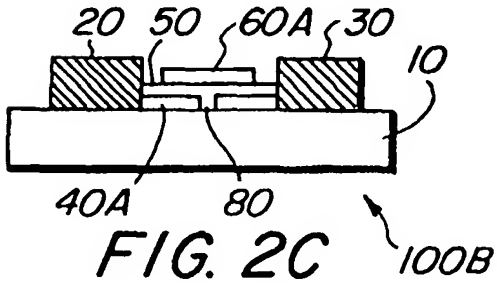


FIG. 2C

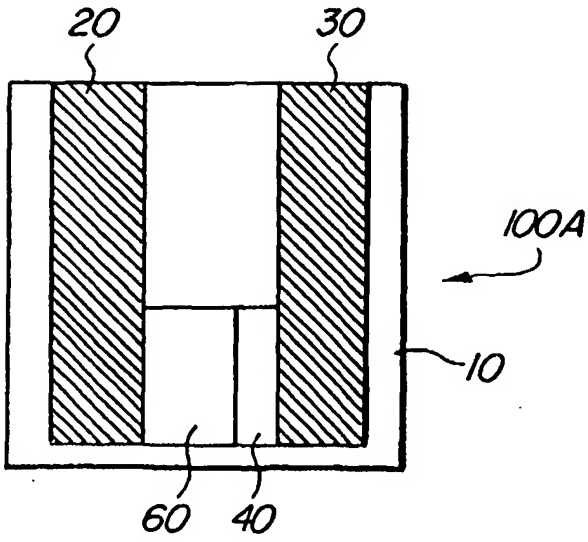


FIG. 1D

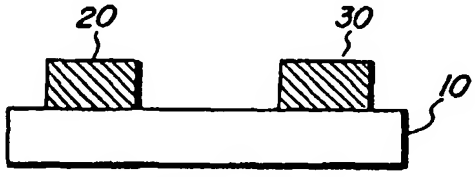


FIG. 3A

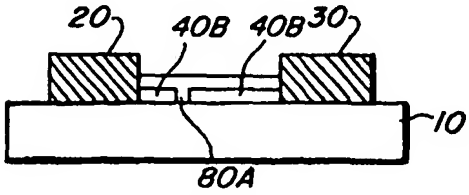


FIG. 3B

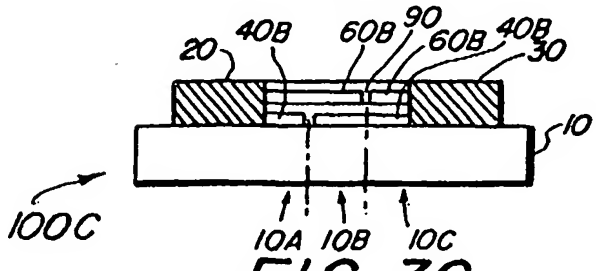


FIG. 3C

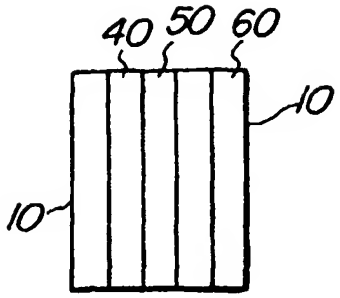


FIG. 4A

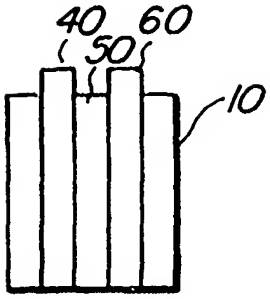


FIG. 4B

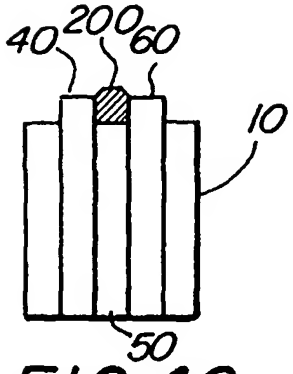


FIG. 4C

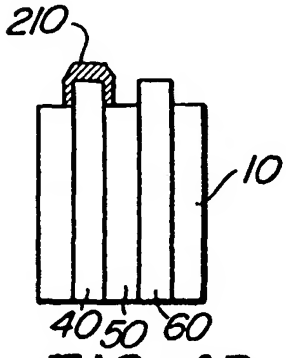


FIG. 4D

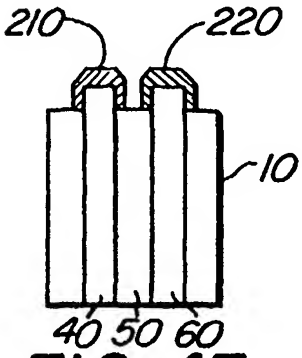


FIG. 4E

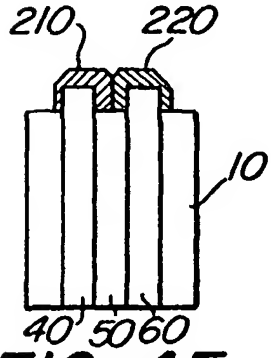


FIG. 4F

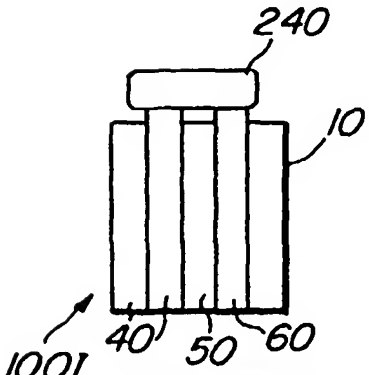


FIG. 4G

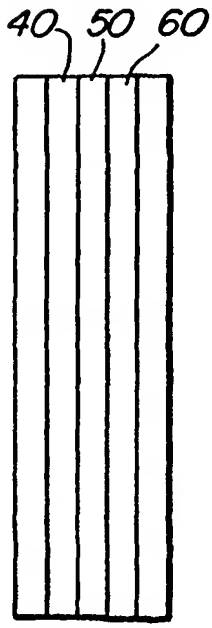


FIG. 4H

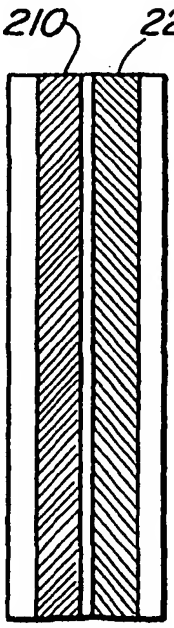


FIG. 4I

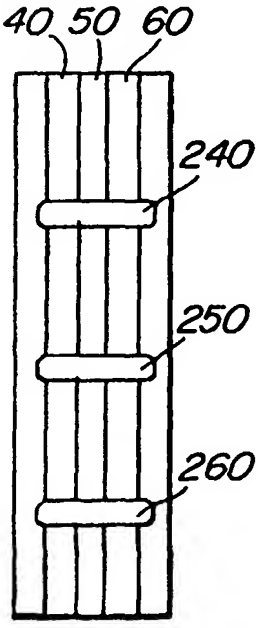


FIG. 4J

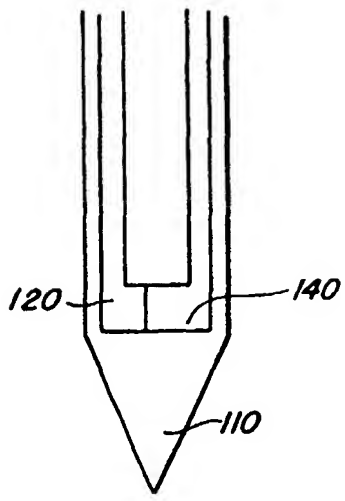


FIG. 5A

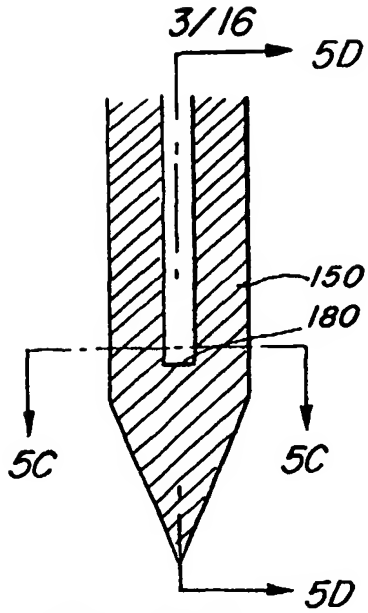


FIG. 5B

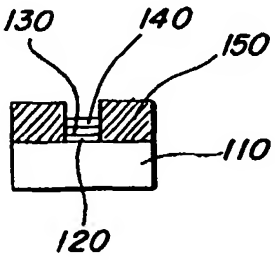


FIG. 5C

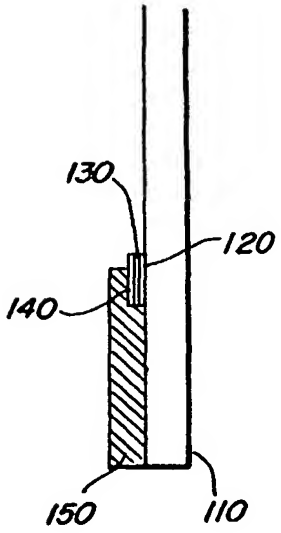


FIG. 5D

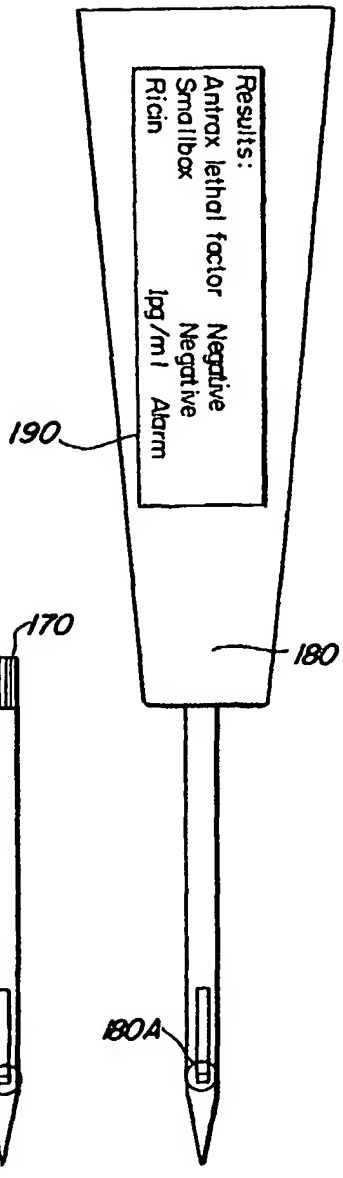


FIG. 5E FIG. 5F

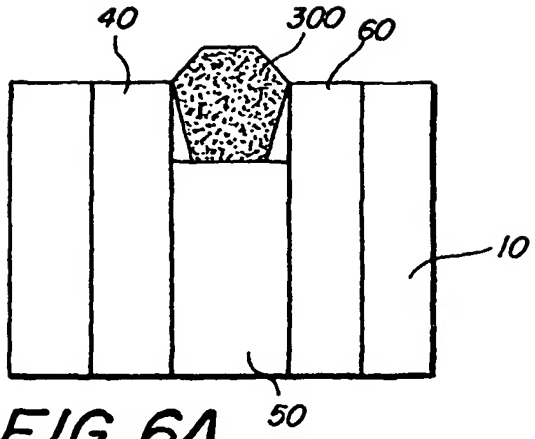


FIG. 6A

H_2

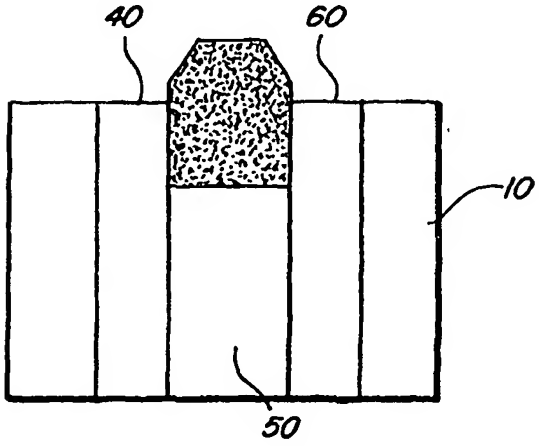


FIG. 6B

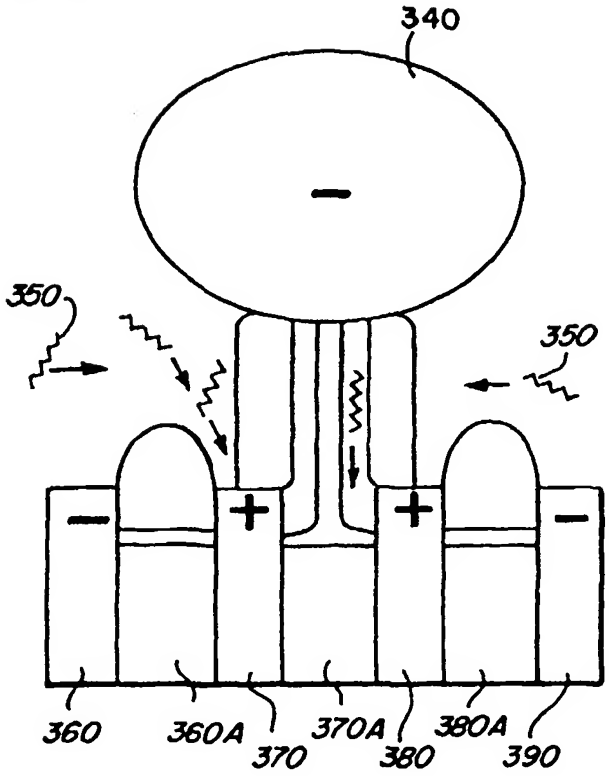


FIG. 7A

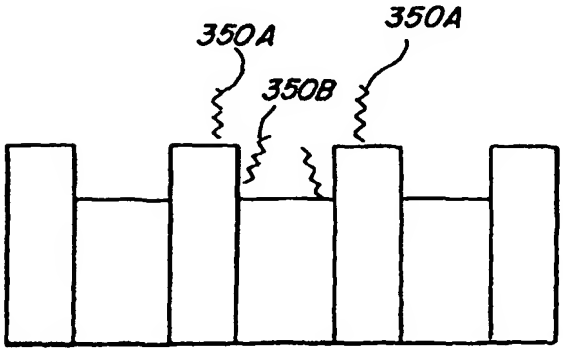


FIG. 7B

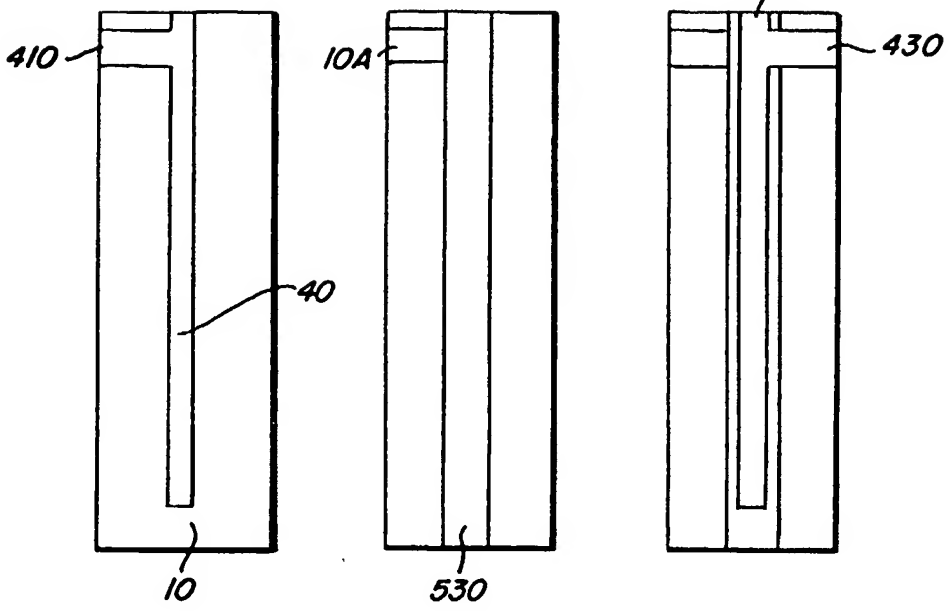


FIG. 8A FIG. 8B FIG. 8C

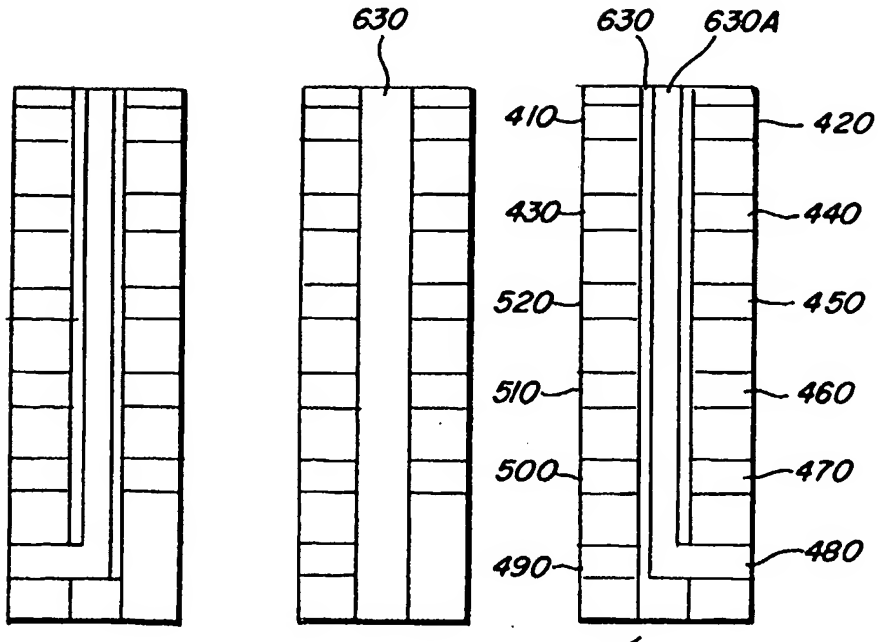


FIG. 8D FIG. 8E FIG. 8F

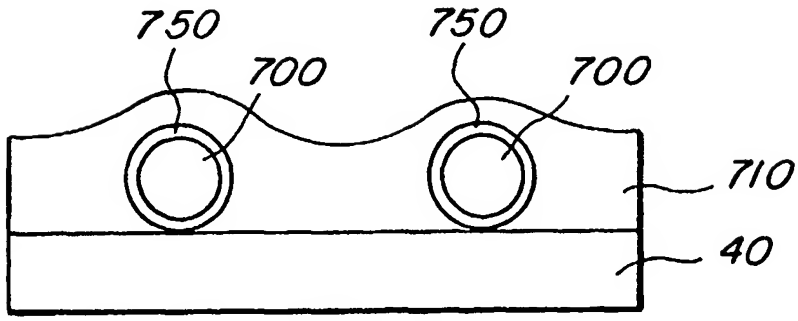


FIG. 9A

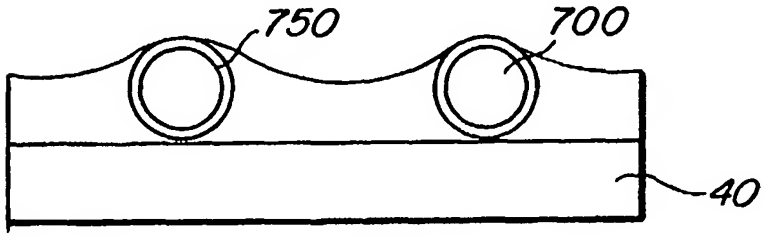


FIG. 9B

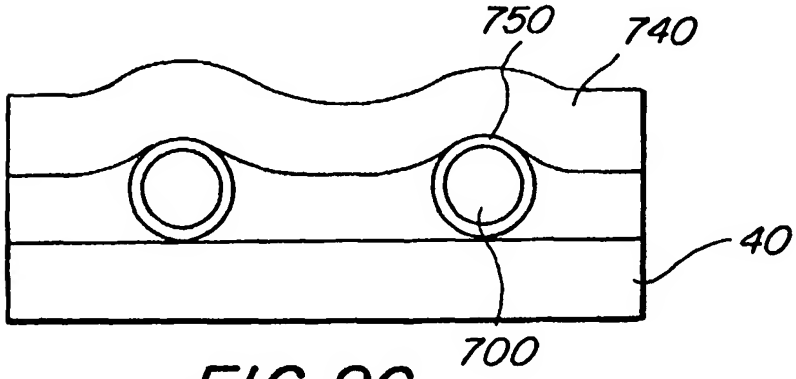


FIG. 9C

FIG. 10A

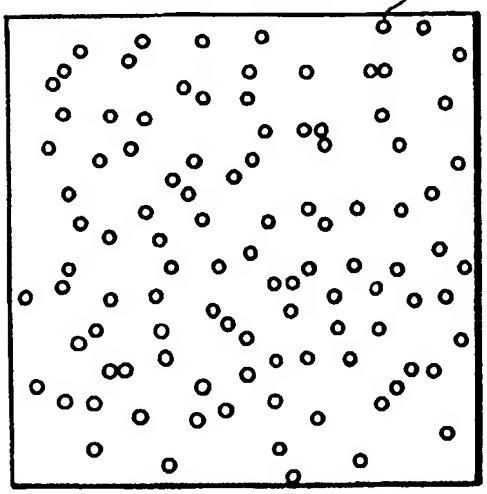


FIG. 10B

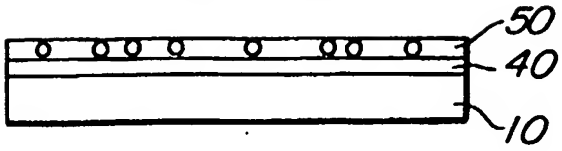


FIG. 10C

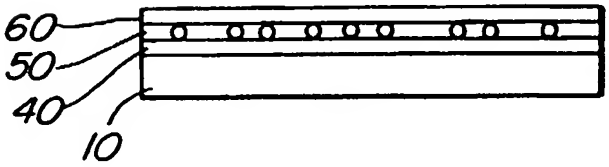


FIG. 10D

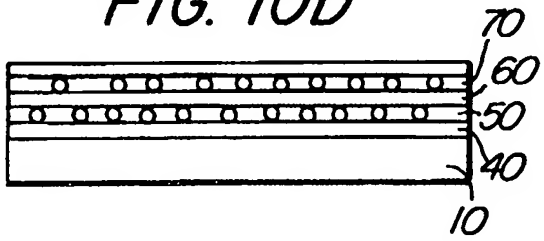


FIG. 10F

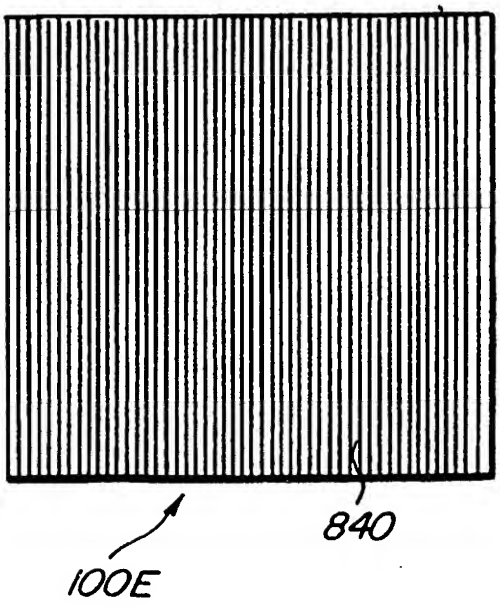


FIG. 10E

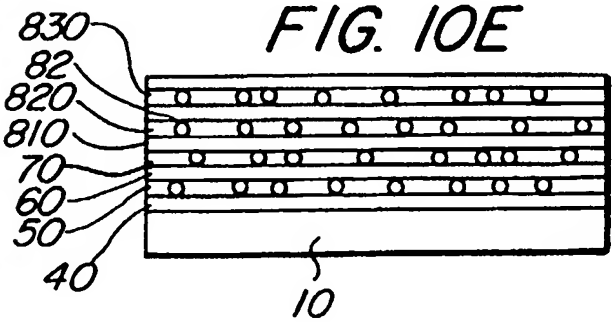


FIG. 11A

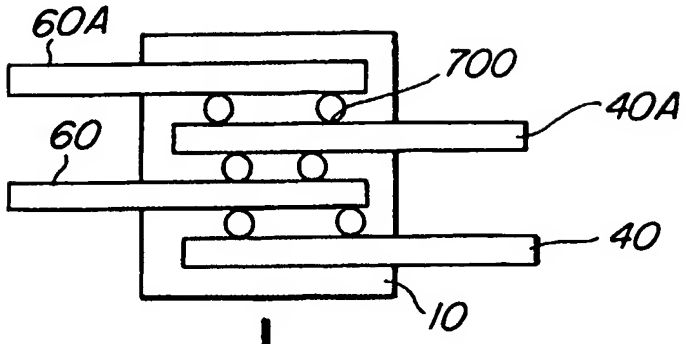


FIG. 11B

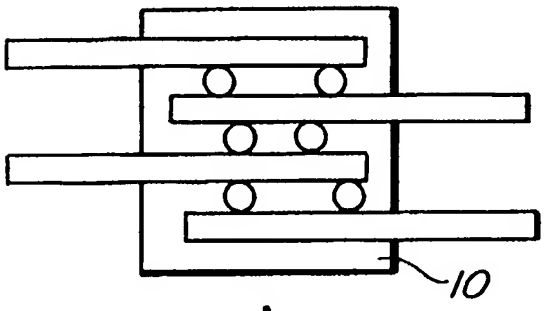


FIG. 11C

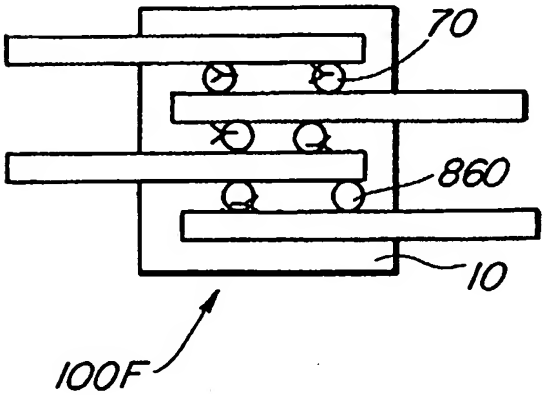


FIG. 12A

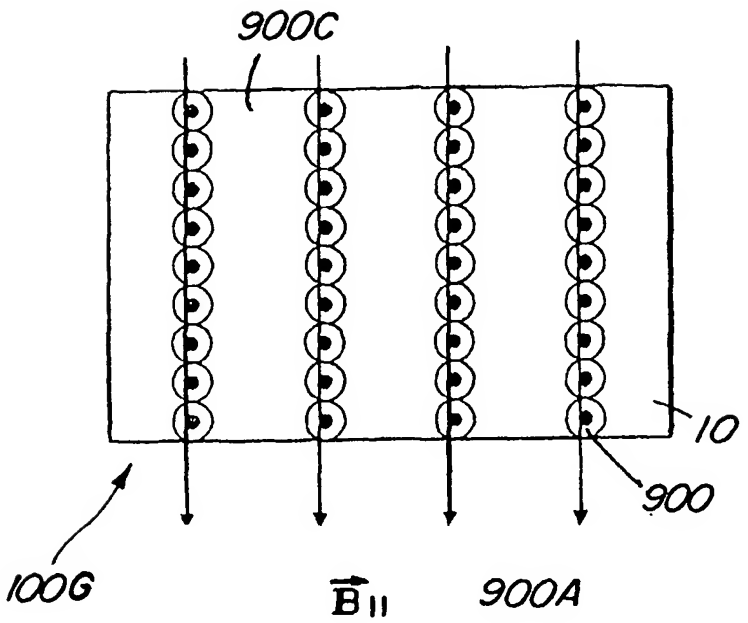


FIG. 12B

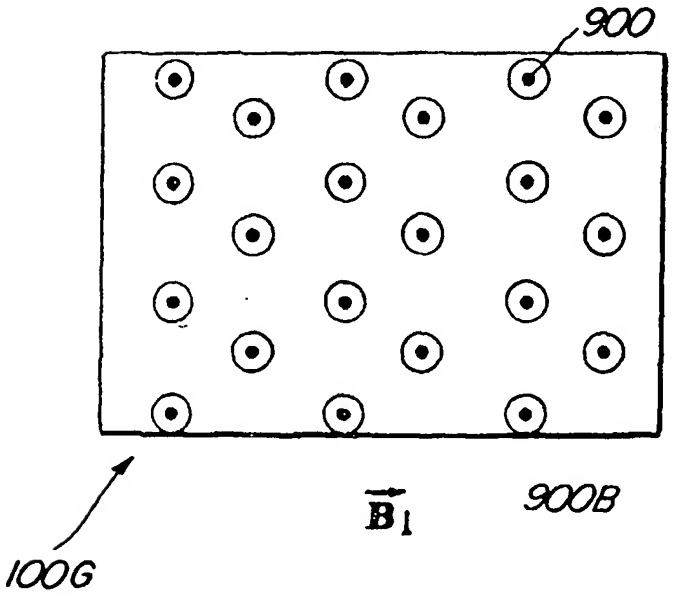


FIG. 13A

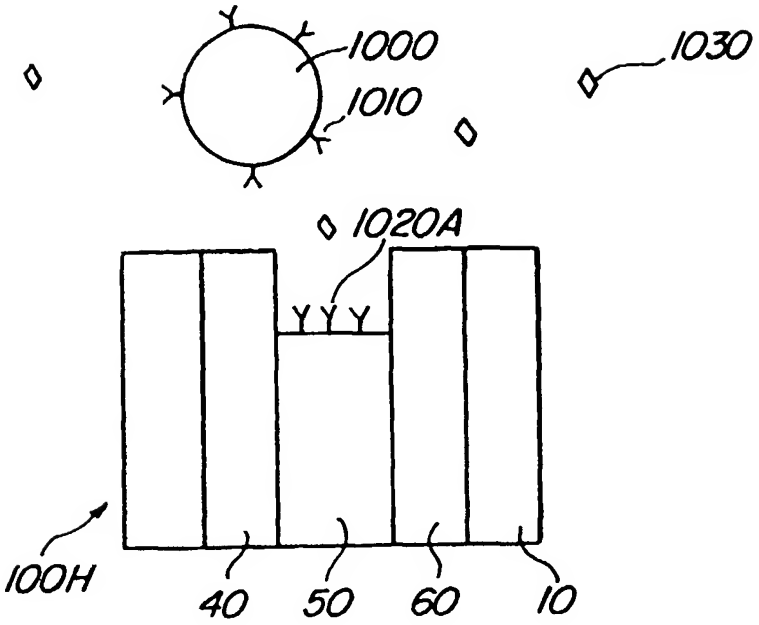


FIG. 13B

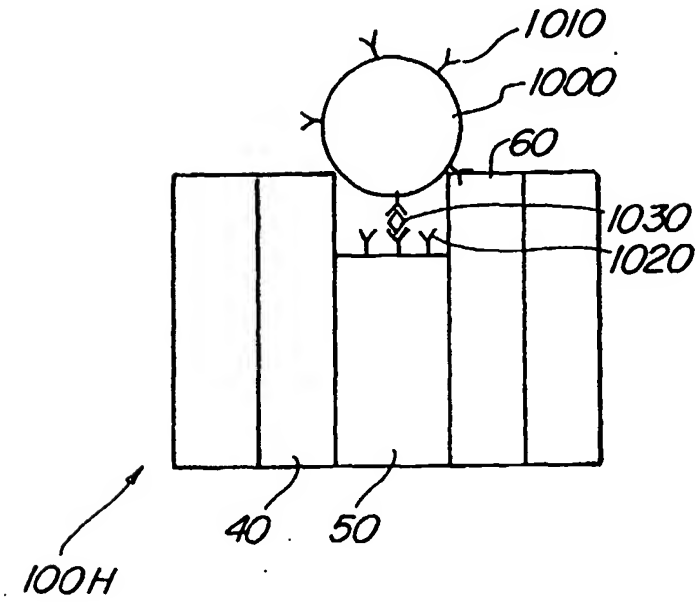


FIG. 14A

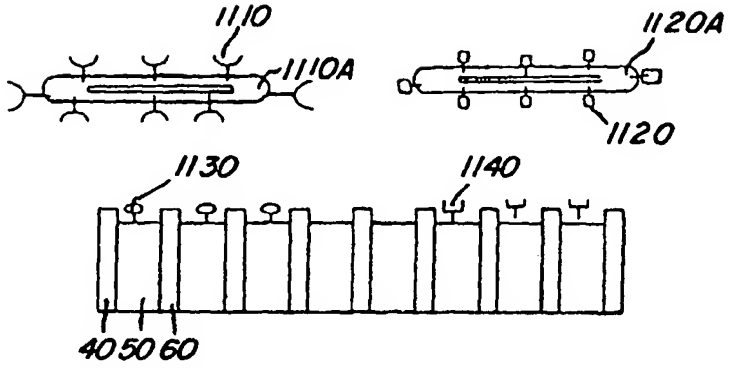


FIG. 14B

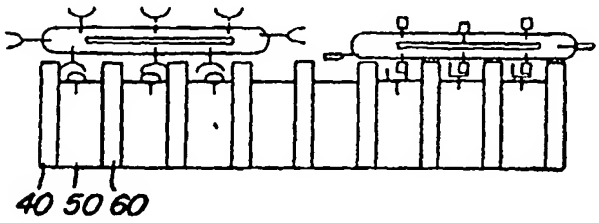


FIG. 14C

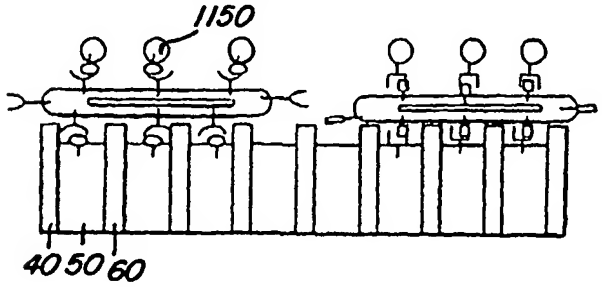


FIG. 14D

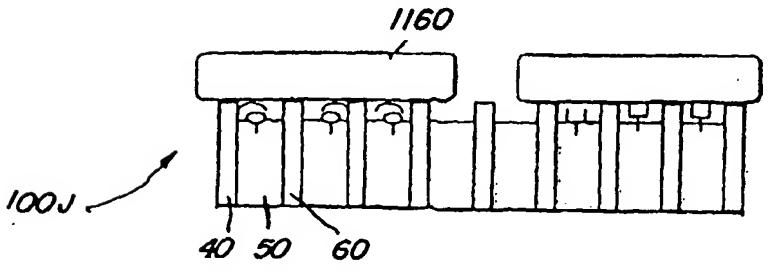


FIG. 15A

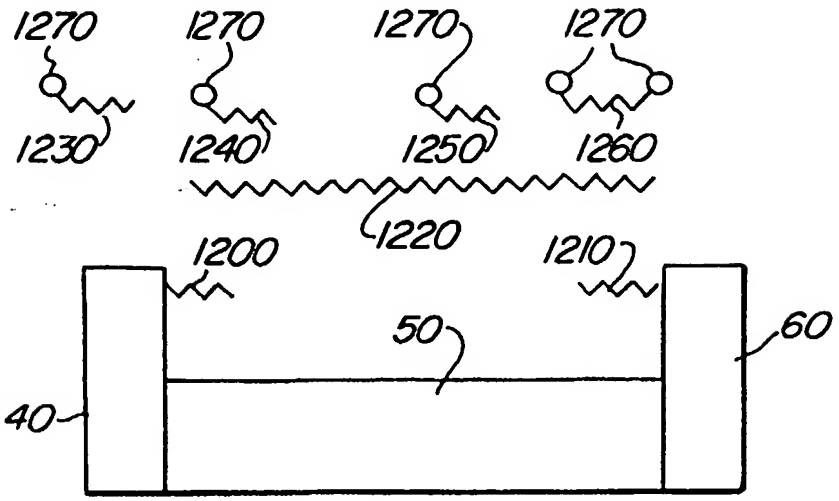


FIG. 15B

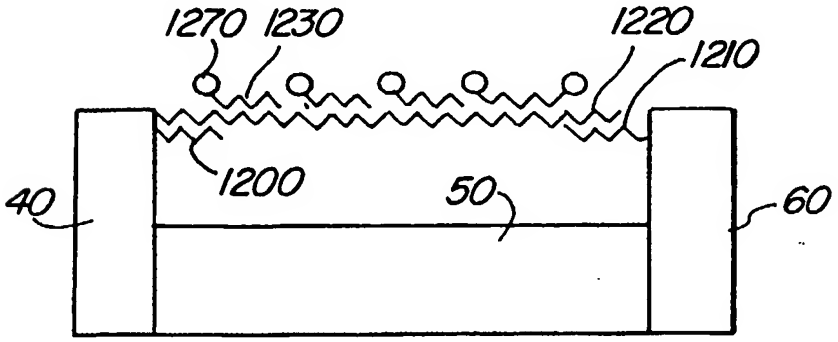
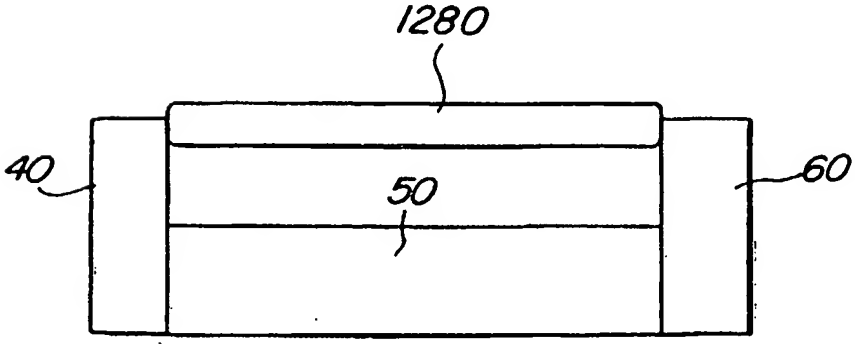


FIG. 15C



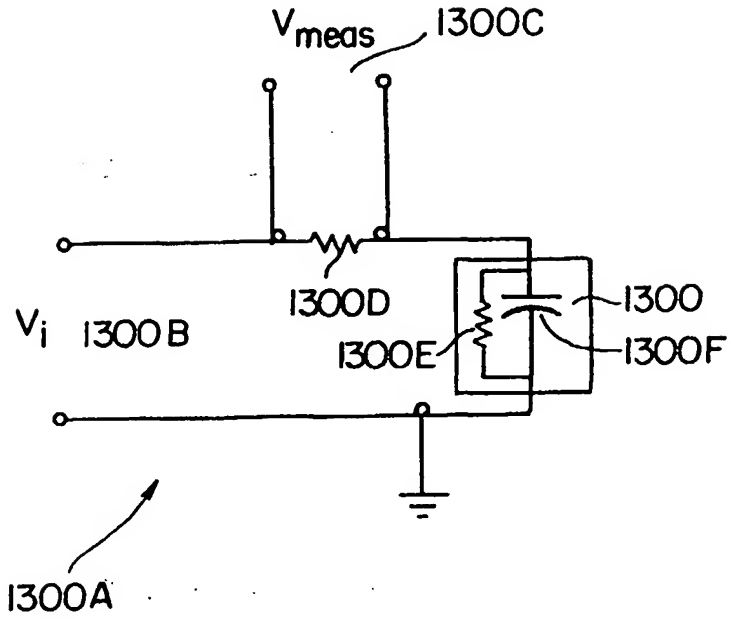

Vmeas
1300C
1300D
1300
Vi 1300B
1300E
1300F
1300A

FIG. 16

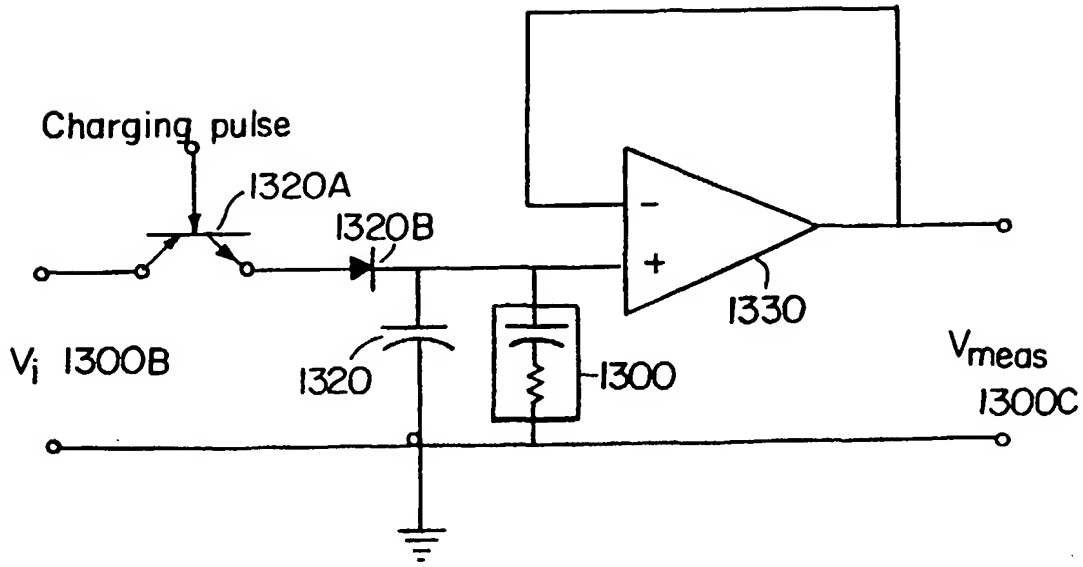

Charging pulse
1320A
1320B
1330
Vi 1300B
1320
1300
Vmeas
1300C

FIG. 17

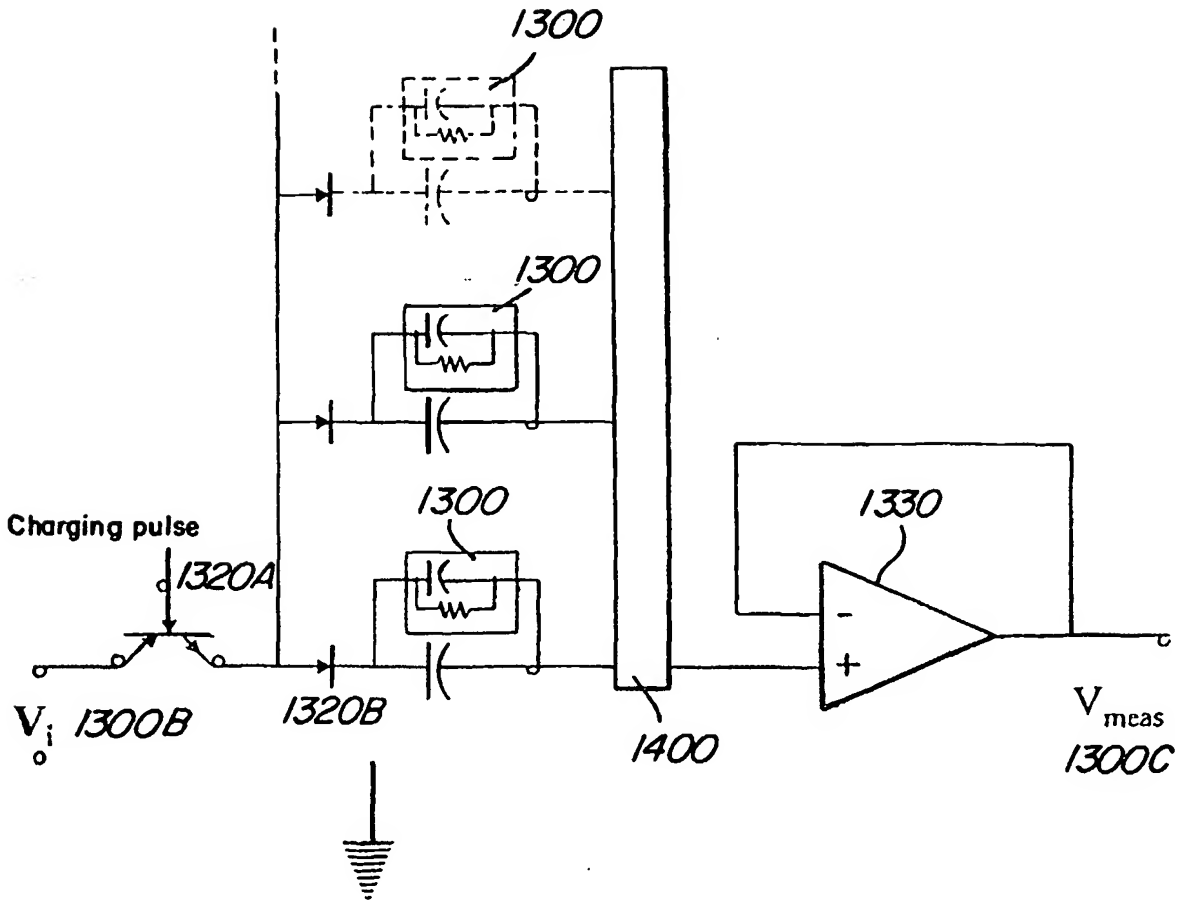
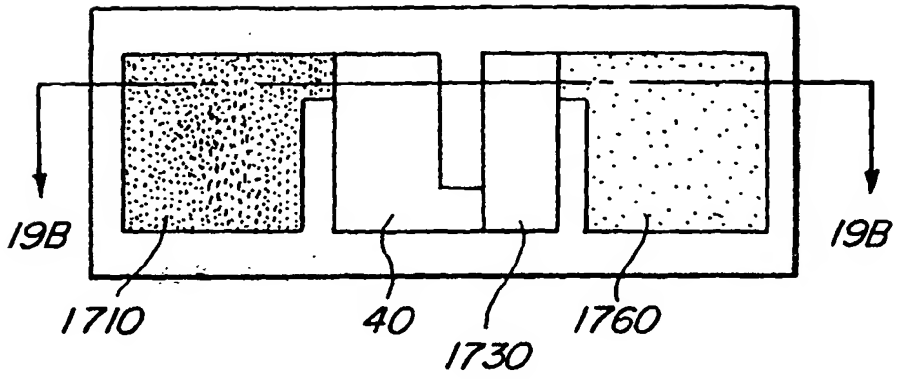

1300
1300
1300
Charging pulse
1320A
1330
V_i
1300B
1320B
1400
V_{meas}
1300C

FIG. 18

FIG. 19A



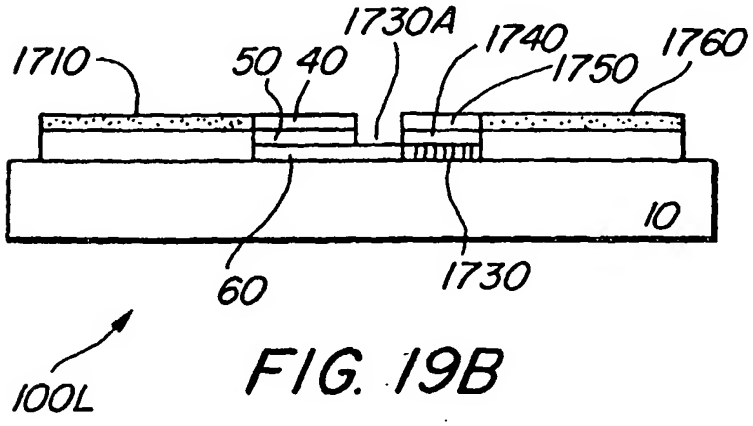


FIG. 19B

FIG. 20A

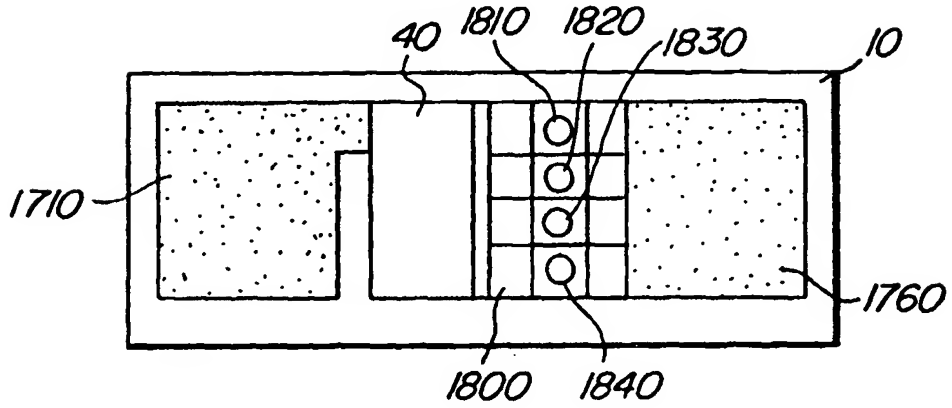


FIG. 20B

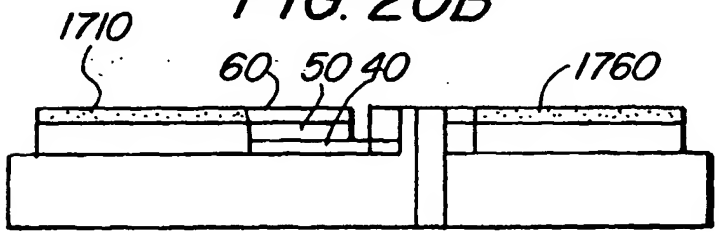
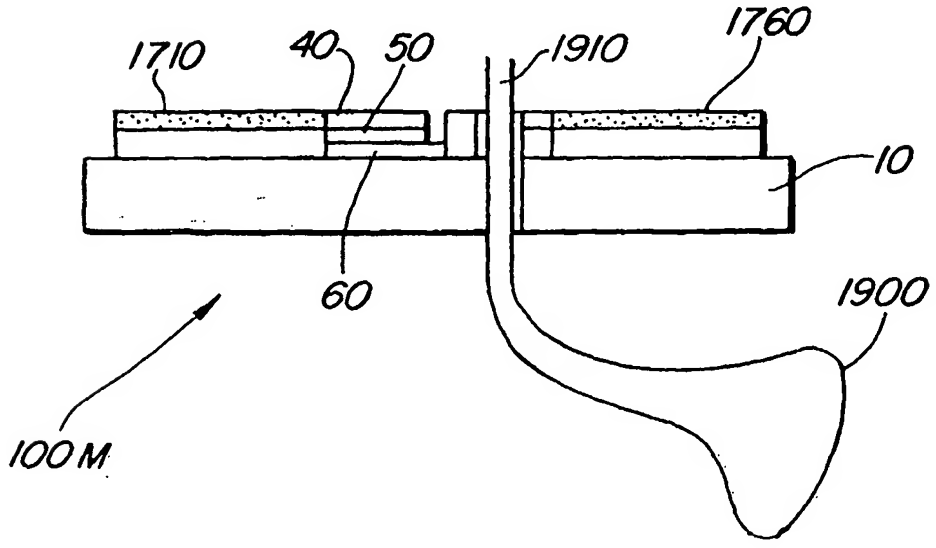


FIG. 20C



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/39937

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : H01L 21/00; C12M 1/34, 3/00
US CL : 438/1; 435/287.1, 287.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 438/1; 435/287.1, 287.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,922,537 A (EWART et al) 13 July 1999 (07.13.1999), Fig 1A, Table 1.	1-13, 19-24, 26-27 ---------- 15-17, 25, 28
X --- Y	US 5,082,627 A (STANBRO) 21 January 1992 (21.01.1992), Fig. 1, cols. 3-6.	1-13, 19-24, 26-27 ---------- 15-17, 25, 28
Y	US 6,060,023 A (MARACAS) 09 May 2000 (09.05.2000), Abstract, Fig. 2.	16-17, 28
Y	US 4,218,298 A (SHIMADA et al) 19 August 1980 (19.08.1980), paragraph bridging cols. 5-6.	25
Y -- A	US 5,580,794 A (ALLEN) 03 December 1996 (03.12.1996), col. 9, lines 55-67	15 -- 18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 2003 (15.04.2003)	14 MAY 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Amir Zarabian Telephone No. 703-3080956

Deborah P. Vega
Paralegal Specialist
Technology Center 2800
(703) 308-3078

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/39937

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 14
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 14 includes the range "3-5000" but does not specify what parameter is described by the range.

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.